Antithrombotic strategies and the impact of coronary reocclusion in ST-elevation myocardial infarction

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Ter nagedachtenis aan mijn vader
Voor Mam

PART 1 Background

CHAPTER 1

General introduction

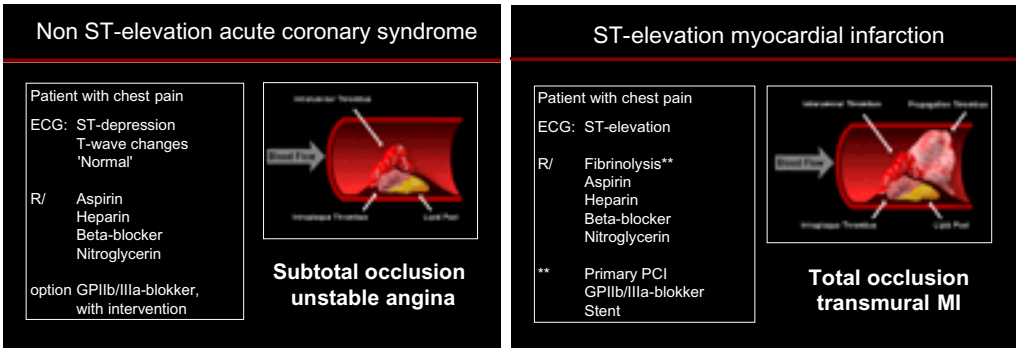

Figure 1 Acute coronary syndromes – coronary pathophysiology and corresponding treatment

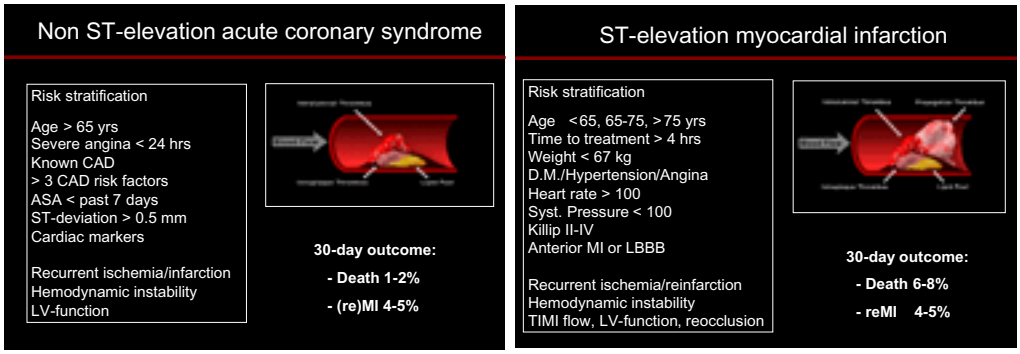

Figure 2 Acute coronary syndromes – risk stratification

The patient with acute chest pain forms one of every day's clinical challenges for the cardiologist. Early diagnosis and triage are of paramount importance to determine the corresponding treatment, especially in the case of a suspected acute coronary syndrome. This thesis focuses on one particular subset of patients, those with an ST-elevation myocardial infarction.

This diagnosis represents not merely an electrocardiographic difference from non ST-elevation acute coronary syndromes, but also implies pathophysiological differences which translate into a different prognosis, the use of additional antithrombotic treatment modalities, and a risk stratification based on (partly) other clinical and angiographic variables.

The general introduction will cover some of the basic background information on ST-elevation myocardial infarction and several specialistic clinical and angiographic items frequently used throughout this manuscript and not explained in detail in the different papers. The outline to the thesis will shortly highlight the study questions addressed in the respective chapters and will put these in both a clinical and scientific perspective.

Acute coronary syndromes, pathophysiology

Acute or subacute coronary thrombosis on a ruptured atherosclerotic plaque forms the classical pathophysiological concept in the etiology of an acute coronary syndrome. After rupture of the plaque, subendothelial matrix such as collagen and a varying amount of lipid core is exposed, after which a cascade of reactions evolves. The resulting thrombusdeposition may cause a subtotal or total occlusion of the coronary artery, which impairs oxygen supply to the coronary bed (1).

In the case of a non ST-elevation acute coronary syndrome some perfusion to the myocardium is still present in the majority of patients, whereas a total occlusion is most frequently the cause of an ST-elevation myocardial infarction. Inherent to these pathophysiological differences are the different approaches with respect to triage, treatment and the risk assessment in the long-term (Figures 1 and 2).

ST-elevation myocardial infarction, treatment

The principal treatment difference as compared to patients with a non ST-elevation acute coronary syndrome is dictated by the absence of coronary perfusion in the case of ST-elevation myocardial infarction: Reperfusion should be achieved as quickly as possible to salvage the jeopardized myocardium (2).

Recanalization by primary percutaneous intervention, using a wire to cross the occlusion and an inflatable balloon for mechanical dilatation of the residual stenosis is one form of reperfusion therapy. Nowadays, stents are often used to prevent acute complications and restenosis. The majority of patients is still treated with pharmacological reperfusion therapy, known as thrombolytic therapy, or, more correctly referred to as fibrinolytic therapy. These agents target the fibrin network, the key determinant of a durable, strong clot.

Pooled analysis of randomized trials has demonstrated that the benefit of fibrinolysis in the first hour is exponentially related to the time from symptom onset (3), whereas after this first golden hour the number of lives saved decreases, and is near linearly related to the time to treatment (Figure 3). These observations fuel the interest in the concept of prehospital fibrinolysis programs, which are overall associated with a gain in time to treatment of about one hour (4). In the Nijmegen region here in the Netherlands, two thirds of patients is treated within 2 hours of symptom onset, and one quarter in the first golden hour (5).

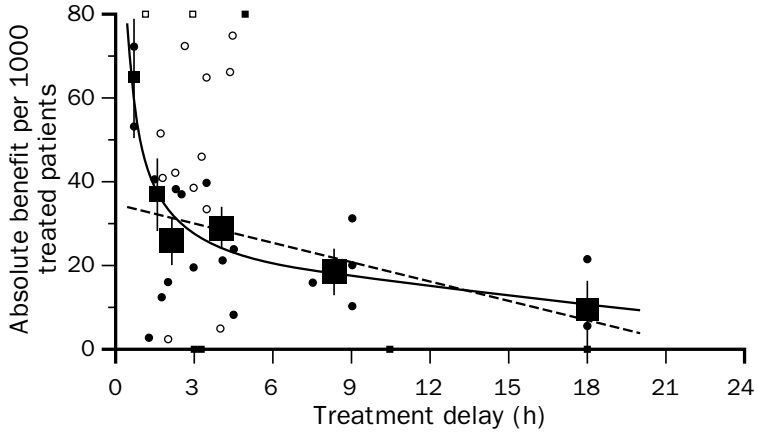

Figure 3 Time to treatment and numbers of lives saved after fibrinolysis data from randomized controlled trials with > 100 patients

As adjunctive to fibrinolytic therapy, antithrombotic agents are needed, both for the facilitation/optimization of reperfusion therapy and the prevention of recurrent ischemic events in the long-term.

The additional antithrombotic agents used in the (sub)acute and chronic phase are:

1. Anti-platelet agents, inhibiting adhesion and/or aggregation of thrombocytes. The mechanism may vary from an effect on cyclo-oxygenase 1, the ADP-receptor, or the glycoprotein IIb/IIIa receptor. Examples are aspirin, dipyridamole and clopidogrel, and abciximab.
2. Anticoagulants, with the following subclassification:
   - Indirect thrombin inhibitors, such as unfractionated heparin and the low-molecular-weight heparins.
   - Direct thrombin inhibitors, such as hirudin, hirulog (intravenous) and ximelagatran (oral).
   - Vitamin K antagonists, often referred to as oral anticoagulants, such as warfarin and coumarin.

Most of the antithrombotic agents have been extensively tested for both types of acute coronary syndromes (6,7). As for the anti-platelet agents, the safety and efficacy of clopidogrel have not yet been established after fibrinolysis. Of the anticoagulants, the use of oral direct thrombin inhibitors can not yet be recommended in lack of sufficient trials.

Important angiographic and clinical characteristics

Whereas history, physical examination and the electrocardiogram provide important information for clinical risk stratification (8,9), the key correlates in the prediction of survival after ST-elevation myocardial infarction are early infarct artery patency and indicators of left ventricular function, the ejection fraction and systolic volume index in particular (10,11).

TIMI flow in the infarct artery

In view of the importance of early realization of brisk, antegrade flow in the infarct artery in as many patients, as early as possible, this qualitative scoring system was

developed to validate comparisons between different fibrinolytic agents in their efficacy on this endpoint: The TIMI flow grading system (12).

This classification of the quality of epicardial flow has been proven to be one of the strongest prognostic indicators (11,13), with 30-day mortality rates varying from 8-10% in the case of failed reperfusion (TIMI flow grades 0-1) to 3-4% for patients with successful reperfusion (TIMI flow grade 3), as assessed 90 minutes after fibrinolysis.

With the increasing number of large scale angiographic trials initiated by study groups from the United States this scoring system has gained general acceptance over the past ten years.

The classification proposed by the European Cooperative Study Group (14), which was used until the late 1980s and early 1990s, has lost its value for the evaluation in future trials. Yet, TIMI flow grade 0 represents the same as ECSG grade 5, and thus, data on this specific endpoint reflect the same and can be easily compared between different trials or used for pooled analyses. As can be deduced from Tables 1 and 2, ECSG grade 4 will merely represent TIMI grade 1 flow, but also some cases of TIMI grade 2 flow.

In the APRICOT-trials all patients entered the study with good coronary flow. In APRICOT-1 inclusion occurred with ECSG grades 0-3, in APRICOT-2 in the case of TIMI grade 3 flow. In APRICOT-1 reocclusion was defined as ECSG grade 4 and 5 (15). At follow-up angiography the infarct artery showed a culprit stenosis of more than 99% and did not, or not completely fill within 3 cardiac cycles. In APRICOT-2, reocclusion was defined as TIMI grades 0-2 flow: total coronary occlusion, or filling distal to the obstruction at a rate perceptibly slower than proximal of the obstruction, or slower than in another coronary artery (16).

Classifications of coronary artery patency

Table 1 European Cooperative Study Group classification

Stenosis grade	
0	Normal
1	< 50% diameter stenosis
2	50% to 90% diameter stenosis
3	91% to 99% diameter stenosis, complete filling within 3 cycles
4	91% to 99% diameter stenosis, no complete filling within 3 cycles
5	Total occlusion with or without collateral filling

Table 2 TIMI flow grading system

TIMI 0	No perfusion: there is no antegrade flow beyond the point of occlusion
TIMI 1	Penetration without perfusion: The contrast material passes beyond the area of obstruction but "hangs" up and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence
TIMI 2	Partial perfusion: The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel – e.g. the opposite coronary artery of the coronary bed proximal to the obstruction
TIMI 3	Complete perfusion: Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery

Reocclusion and reinfarction

A second angiographic parameter, which has only been studied by a few research groups over the world, is reocclusion. This is partly due to the required sequential angiographies, one showing an open infarct artery after reperfusion therapy, the second demonstrating subsequent occlusion. Methodologically even more correct, a third angiography would be required that shows an occluded infarct artery before fibrinolysis. Yet, now that the need for early restoration of coronary patency has been unequivocally demonstrated over the years, and intravenous fibrinolysis has replaced the initial intracoronary administration, this initial angiography can not be peformed anymore nowadays (17).

Of the clinical prognostic indicators during the index admission, reinfarction after fibrinolysis is associated with a twofold increased risk of mortality. Half of these reinfarctions occur within 48 hours after reperfusion therapy (18), and are often attributed to infarct artery reocclusion (17,19). Given their profound impact, reinfarction forms one of the main endpoints to compare antithrombotic regimens, despite the often cumbersome definition of this endpoint, especially early after fibrinolysis. Reocclusion has been shown to occur without clinical signs of reinfarction in about half of cases (19-22), and, even in the absence of clinical reinfarction, impaired recovery of left ventricular function has been demonstrated (23). Despite the potential prognostic consequences of these reocclusions, few studies have addressed this issue.

The present thesis therefore primarily focuses on reocclusion, encompassing both reinfarction, and the 'silent' occlusions which interfere with left ventricular recovery after myocardial infarction.

Recurrent ischemia and revascularization

After fibrinolytic therapy, recurrent ischemia either at rest or during stress testing indicates an increased risk for unstable angina, reinfarction and mortality during follow-up (24). This forms the rationale for an ischemia-guided revascularization strategy. Both reinfarction and recurrent ischemia are often caused by recurrent (sub)total thrombosis. More potent antithrombotic regimens might therefore reduce these complications.

Another approach that has been advocated is a more aggressive revascularization strategy. In that case patients after fibrinolysis undergo routine catheterization, irrespective of symptoms and/or recurrent ischemia, and subsequently, angioplasty

will be performed or bypass surgery planned. As of to date, such a routine invasive strategy has not resulted in better outcome than an ischemia-guided approach. An increased risk of periprocedural infarctions has been postulated as the explanation for this lack of benefit (25).

Most of the evidence, however, reflects data from randomized trials performed in the late 1980s and early 1990s and is not representative for current interventional cardiology with the introduction of glycoprotein-receptor blockers and stents to reduce periprocedural events and restenosis, respectively.

Still, an angiographic follow-up study performed in the same era as the old trials suggested that a high grade stenosis does not predict reinfarction (19), which questions the need of a routine invasive approach. In fact, several observations have shown that reinfarction often occurs on previously less severe lesions (27). On the other hand, in most of the randomized trials to date angioplasty was restricted to the severe lesions, whereas incorporating dilatation of less severe lesions might be beneficial.

Unfortunately, angiographic follow-up was not performed in the randomized studies on a routine invasive approach, and reocclusion was not addressed. The trials only focused on the clinical endpoint reinfarction. Several studies have demonstrated that stenosis severity does predict reocclusion, and thus, a potential benefit on this endpoint, and, for example, left ventricular function, may have gone undetected. Clinical events in these trials were followed for one year, which may have been too short to detect a benefit exerted through these mechanisms.

In view of the above, the APRICOT-trial having paired angiography in 87% of patients provides a unique opportunity to further unravel the relationship between reocclusion, reinfarction and stenosis severity, and may as such contribute to insights that may be valuable for the design and protocol of future randomized studies on the impact of a routine invasive strategy. Moreover, clinical follow-up information has been collected for more than ten years, which will provide insight into the prognostic impact of late reocclusion, with special interest in the clinically silent reocclusions. If indeed late reocclusion is associated with adverse long-term survival, the randomized trials on more aggressive revascularization regimens might incorporate reocclusion as one of the endpoints.

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CHAPTER 2

Outline to the thesis

In **Chapter 3** a general overview is presented regarding the evolutions in the treatment of ST-elevation myocardial infarction, varying from development of new fibrinolytics and combined pharmacological reperfusion regimens to the use of new adjunctive antithrombotic agents.

Chapter 4 addresses the impact of two different antithrombotic strategies: it concerns a randomized comparison of early prehospitally initiated fibrinolytic therapy with a strategy of in hospital initiated fibrinolysis, and is one of the few studies assessing the long-term outcome after these two reperfusion strategies. This study is known under the acronym MITI. In an additional analysis patients treated within the golden hour are compared to those treated later.

In **Chapter 5** we performed the first long-term follow-up study in which patients with reocclusion were compared to those with sustained infarct artery patency in the 3 months after fibrinolytic therapy. In view of the detrimental impact on left ventricular contractile recovery, 3-year survival rates were compared between groups, as well as recurrent ischemic complications.

Chapter 6 describes the only randomized placebo-controlled angiographic follow-up study to date addressing the impact of anti-platelet therapy on coronary artery disease progression in the non-infarct arteries. Although the effect of aspirin is most outspoken early after ST-elevation myocardial infarction, it has also been proven beneficial when started up to six months after the event, after which recurrent events are not as often related to the infarct artery as in the acute phase. It was therefore hypothesized that part of the long-term benefit of aspirin might be attributed through reduced progression of coronary artery disease in the non-infarct arteries.

Given the adverse consequences of reocclusion and its incidence of about 25-30% in the first year after myocardial infarction, better preventive strategies are warranted. **Chapter 7** describes the randomized angiographic follow-up trial APRICOT-2, in which a prolonged, combined antithrombotic strategy of both anti-platelet and anticoagulation therapy is tested against a standard 48 hour anticoagulation regimen and the indefinite use of aspirin.

Chapter 8 presents the collective evidence to date on the combination of oral anticoagulation therapy and aspirin. In addition to the moderately sized, mechanistic, angiographic follow-up studies, all clinical trials on this issue are reviewed, and important aspects for the implementation in daily clinical practice are discussed.

The analysis in **Chapter 9** aims to provide insight into an important issue with regard to the lack of benefit of a routine invasive strategy after fibrinolysis to improve outcome in terms of death and reinfarction. With stenosis severity being a strong predictor of reocclusion, reinfarction rates were expected to be reduced by a routine invasive strategy. Previously, a meta-analyses on the impact of a routine invasive strategy showed an increased risk of periprocedural events, and outcome was not better than after an ischemia guided revascularization strategy. However, an angiographic follow-up study performed in the same era as these trials, suggested that recurrent ischemic events were not associated with the residual stenosis severity. With APRICOT being conducted in that same period, we intend to further elucidate the relationship between the residual stenosis severity, reocclusion and reinfarction. Does the increased risk for reocclusion associated with a severe residual stenosis also translate into an increased risk for reinfarction, when compared to patients with a low-medium grade residual lesion?

In **Chapter 10** a 10-year clinical follow-up study is presented on the patients that participated in the APRICOT-1 trial, investigating whether late coronary patency is associated with cardiac survival, independent of left ventricular function. Whereas the impact of early reinfarction and reocclusion are undisputed, conflicting data have been reported on the prognostic consequences of late coronary patency. This is the first angiographic follow-up observation describing the impact of late coronary patency after fibrinolysis in the setting of an ischemia guided revascularization strategy.

Chapter 11 and 12 summarize the main outcomes of the presented analyses and provide implications both for daily clinical practice and for future (angiographic follow-up) trials after ST-elevation myocardial infarction.

PART 2 The thesis

CHAPTER 3

Adjunctive therapy in patients treated with thrombolytic therapy

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Heart 2004;90:581-588

Introduction

Thrombotic occlusion of an epicardial coronary artery has been implicated as a potential mechanism involved in acute myocardial infarction in as early as 1910 (W1), and became generally accepted after the landmark report by De Wood et al. in the early eighties. (W2)

In search of pharmacological means to dissolve thrombus so called 'thrombolytics' were developed. These agents target fibrin, the key element in clot-formation, and are therefore more accurately referred to as fibrinolytics. Large clinical trials confirmed the hypothesis that timely restoration of coronary patency had a marked impact on survival after ST-elevation myocardial infarction: ~20-30 lives saved per 1000 patients treated (W3). With the improvements in techniques and experience, mechanical reperfusion therapy has been proven to be even more beneficial than in-hospital initiated fibrinolytic therapy (W4). Yet, pharmacological reperfusion therapy is more widely available, more easily applicable, and less dependent of institutional experience.

Consequently, the majority of patients with ST-elevation myocardial infarction receives fibrinolytic therapy. Given the profound impact of early reperfusion (1), preferably within the first, "golden", hour the initiation of prehospital fibrinolysis programs resulted in benefits in the same order as achieved by primary angioplasty: ~18 lives saved per 1000 patients, when compared to in-hospital fibrinolysis (2). New pharmacological reperfusion strategies to achieve patency rates that could more favorably compare with those achieved by primary angioplasty constitute a second initiative. In addition to further optimization of antithrombotic treatment in the acute phase, the experience with anti-ischemic, plaque stabilizing strategies applied in the (sub)acute phase and in the long-term has evolved. The current review presents the latest pharmacological developments and their implications for daily clinical practice in patients with acute ST-elevation myocardial infarction (Figure 1).

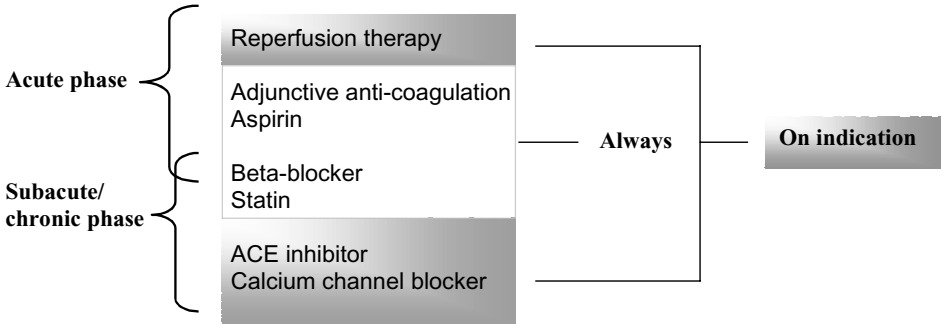

Figure 1: Schematic representation of the currently recommended pharmacological treatment strategy in acute myocardial infarction patients.

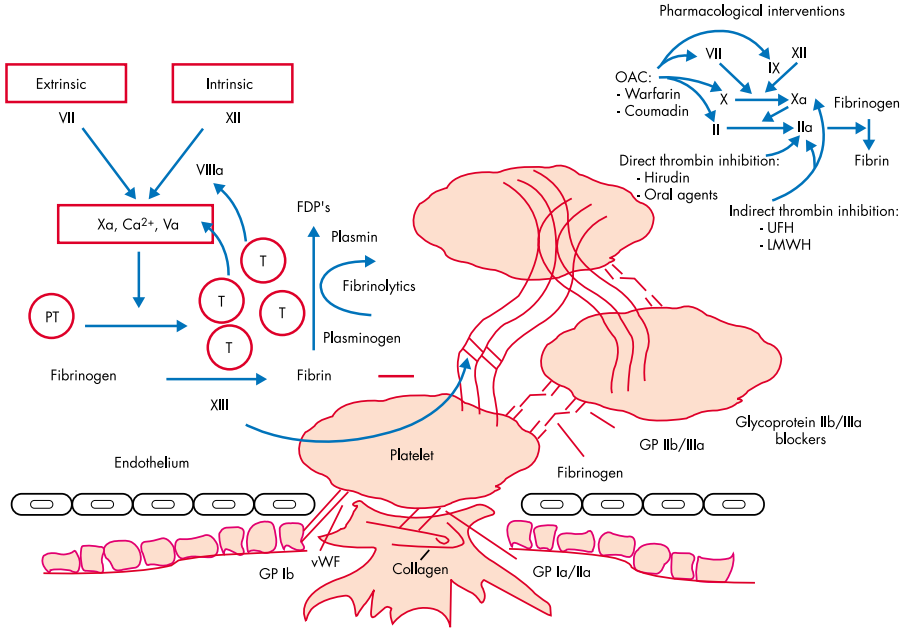

Figure 2: Modified figure adapted from reference 5.
Thrombus formation and pharmacological interventions in the coagulation cascade – Interaction of platelet aggregation (fibrinogen, GPIIb/IIIa) and activation of the coagulation cascade results in the thrombin-induced formation of a fibrin-rich clot. Fibrin cross-linking by factor XIII improves clot-strength. Whereas oral anticoagulants interfere with the production of coagulation factors, other agents inhibit the action of activated clotting factors. Fibrinolytics target the degradation of fibrin, mediated through plasmin.
vWF = von Willebrand factor; PT = prothrombin (II);T = thrombin (IIa); OAC = oral anticoagulants; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; FDP's = Fibrin degradation products

Strategies to enhance coronary patency - The acute and subacute phase –

From the very first randomized trials with fibrinolytic agents, angiographic (sub)studies demonstrated the concept of early restoration of coronary patency, better preservation of left ventricular function and improved survival (3). Secondly, the adverse consequences of reocclusion of the infarct artery were demonstrated in terms of impaired recovery of left ventricular function and higher rates of mortality and recurrent ischemic events (4).
In order to optimize the efficacy of reperfusion therapy, concomitant thrombin and platelet inhibiton is required, not only aiming at enhanced early patency but also to reduce reocclusion and recurrent thrombotic events.

Pathophysiological rationale

Acute thrombotic occlusion of an epicardial artery is often initiated by plaque rupture or erosion, after which subendothelial matrix is exposed to the blood. Following vasoconstriction, the initial response to vessel injury, a cascade of events evolves. Platelets adhere to the damaged vessel wall, secrete chemoattractive substances, that result in platelet recruitment and aggregation. Activation of tissue factor (factor VII) is one of the earliest involved responses, stimulating a prompt reaction of the extrinsic and intrinsic coagulation cascade. Thrombin constitutes one of the most important proteins. It has a potent effect on platelet aggregation, and promotes the formation of fibrin, the key element in the formation of a durable strong clot (5). Fibrinolytics induce activation of plasminogen into plasmin, resulting in degradation of fibrin (Figure 2).

Reperfusion strategies

Despite many years of experience with fibrinolytic agents, some crucial aspects will be highlighted below. These concern relevant issues for the clinician's choice of adjunctive treatment, and aspects regarding the rationale for the development of new strategies.

Fibrinolytic therapy, efficacy, Table 1

With a varying survival benefit from ~20 per 1000 patients treated after 4-6 hours to ~50 per 1000 when starting within 1-2 hours of symptom onset, agents that can easily be used in the prehospital setting have always been of interest (1). After the initial success with streptokinase (6,W5), bolus treatment with anistreplase gained attention (W6,W7,W8). A second initiative has been the search for a more potent agent, realizing higher rates of early patency. A third goal constitutes the development of agents with less bleeding complications, which were thought to be related to the lack of fibrin specificity, i.e. the action on both fibrin-bound and circulating plasminogen, inducing systemic depletion of fibrinogen. "Second-generation" agents like rt-PA were produced, but not until the introduction of an accelerated regimen a breakthrough was realized (W9). This regimen resulted in an early and sustained survival benefit as compared to streptokinase, and proved particularly effective in patients with anterior myocardial infarction (7,W10). The strongest predictor of survival was identified as the realization of early brisk, antegrade flow in the coronary artery, so called 90-minute-TIMI-3 flow, seen in 54% of patients on rt-PA versus 32% in those on streptokinase (3). Based on these insights the "third-generation" lytics were manufactured to further improve survival. Yet, despite promising patency data with the bolus agents reteplase and tenecteplase (W11,W12), no additional improvement in clinical outcome was observed (W13,W14).

Fibrinolytic therapy, safety Table 2

The clinically most threatening complication is the risk of intracranial hemorrhage, which varies between trials from 0.4% to 1.1%, dependent on the agent, and the proportion of high risk patients included (7,8,W15,W16,W17). This constitutes a fatal complication in about half of patients, with another third being permanently disabled (7,8,W15). Unexpectedly, fibrin-specific agents increased this complication. Although patient factors are most important, the impact of the intensity of anticoagulation with unfractionated heparin can not be stressed enough. Each 10-second increase of the 12-hour APTT over 70 seconds has been shown to increase the absolute chance of intracranial hemorrhage with 0.07% (9). From past trials it has also been deducted that the dose of fibrinolytic therapy is of paramount importance (W18). This deserves renewed interest with the introduction of weight-adjusted bolus fibrinolytic therapy, given the potential impact of erroneous administration of a higher dose than indicated.

In light of the above, the decision to choose for fibrinolytic therapy, and the choice of agent, should be individually tailored, assessing the potential benefit and harm in the given situation. In lack of better agents, some institutions have primarily changed logistics by implementing prehospital fibrinolysis with a rather liberal rescue angioplasty policy, which resulted in comparable outcomes to primary angioplasty in the recent CAPTIM trial (10). Although the available randomized data support rescue angioplasty (11), a strategy of routine immediate angioplasty after non-fibrin specific agents seems less favorable, which may in part be explained by the increased bleeding risk (W19). In individual cases with persisting pain, heart failure or cardiogenic shock rescue angioplasty should always be considered. The use of glycoprotein IIb/IIIa receptor blockers after streptokinase should be avoided (12), whereas the benefit of its periprocedural use following other fibrinolytics should be carefully weighed against the increased bleeding risk in each case individually.

Half-dose lytic and GPIIb/IIIa-receptor blockade, rationale

The lack of additional clinical benefit from angiographically more potent fibrinolytic regimens questioned the somewhat limited focus on the TIMI-3 flow concept, and broadened the search towards improved strategies. Some postulated increased reocclusion rates as a result of enhanced platelet activation after more fibrin-specific therapy. A second suggestion was that improved epicardial patency per se may not translate into better outcome in the case perfusion at tissue-level is not (fully) restored (W20,W21). Part of this lack of endocardial perfusion might be caused by periferal embolization of platelet-rich clot debris. Importantly, fibrinolytic therapy not only results in fibrin degradation and thrombus dissolution, but also induces platelet aggregation by a thrombin and plasmin-mediated pathway. In ISIS-2 the addition of 35 days of aspirin resulted in improved outcome after streptokinase (6). Therefore, a combination of fibrinolytic therapy and stronger platelet-inhibition was hypothesized to confer additional benefit; not only by the potential to enhance early TIMI-3 flow, but also by the above mentioned mechanisms.

Half-dose lytic and GPIIb/IIIa-receptor blockade, efficacy, Table 3

The first results in angiographic pilot trials studying half dose rt-PA with full-dose abciximab were impressive, with TIMI-3 flow rates at 60 min. comparable to those at 90 minutes achieved with accelerated rt-PA alone (12). This promising regimen has never been tested in a large clinical trial, probably due to the introduction of TNK-tPA. The clinical ASSENT-3 trial evaluated the impact of a combined regimen

with TNK-tPA, which did not affect survival but reduced recurrent ischemia at the cost of higher bleeding rates (13). Data from the angiographic pilot study, published half a year after the clinical trial, showed no improvement in TIMI-3 flow (W22). The second large-scale clinical trial on this subject, GUSTO-V, did not demonstrate a survival benefit either (14). First, it should be realized that the regimen chosen was based on a subgroup-analysis from the angiographic pilot trial SPEED. Whereas the randomized treatment arms showed no clear benefit on TIMI-3 flow, the subgroup of patients on standard dose heparin did (W23). A second explanation results from the lessons learnt from GUSTO-1. To improve survival after pharmacological reperfusion with an absolute 1%, an absolute 20% improvement in TIMI-3 flow is necessary (3,W24). Neither of the discussed regimens, nor the strategies performed with other glycoprotein-blockers met this criterium (W24, W25,W26).

Half-dose lytic and GPIIb/IIIa-receptor blockade, safety, Table 3

A combined regimen, using only half-dose lytic, was expected to reduce the most serious bleeding complication, i.e. intracranial hemorrhage. Yet, findings from GUSTO-V seemed dissapointing at first glance. More thorough analysis, however, showed that patients aged younger than 57 had a reduced risk of intracranial hemorrhage, whereas in those over 57 this risk was increased (W27). Older patients, especially those over 75 years, are a subgroup at particular high risk (14). Similar observations were made in ASSENT-3, with reduced recurrent ischemic events at the cost of higher bleeding, again specifically in the elderly (13).

Despite these somewhat disappointing findings, the combined regimen remains an attractive alternative to full- or half-dose fibrinolysis as pretreatment for facilitated angioplasty for acute myocardial infarction. As TIMI-3 flow before the procedure is a strong predictor of prognosis, the combined treatment strategy might confer benefit, with a door-to-balloon time often exceeding 2 hours (W28). Moreover, the concomitant administration of abciximab could positively impact procedural success at the microcirculatory level. The pending FINESSE and ADVANCE-MI trials address this question in over 8,500 patients with ST-elevation myocardial infarction. As of to date, the described combined regimen can not be recommended for general implementation in daily clinical practice.

Table 1 Current fibrinolytic agents in the treatment of ST-elevation myocardial infarction

	Streptokinase	**Alteplase rt-PA**	**Reteplase r-PA**	**Tenecteplase TNK-tPA**
$T^1/_2$ (min.)	15-25	4-8	11-14	17-20
Allergenic	Yes	No	No	No
Fibrin specific	-	+	+	++
PAI-1 resistent	-	-	-	+
Bolus	No	No	Double	Single
Dosing	1.5 MU over 30-60 min.	15 mg Bolus, followed by 0.75 mg/kg – max. 50 mg – over 30 min. followed by 0.5 mg/kg – max. 35 mg – over 1 hr.	10 U Bolus, twice, 30 min. apart	Weight-adjusted: < 60 kg: 30 mg 60-69 kg: 35 mg 70-79 kg: 40 mg 80-89 kg: 45 mg ≥ 90 kg: 50 mg

PAI = plasminogen activator inhibitor

Table 2 Risk factors for intracranial bleeding following fibrinolysis for ST-elevation myocardial infarction

- Age > 75 years
- Body-weight < 67 kg
- Female gender
- Hypertension
- Previous TIA/CVA
- Inappropriate anticoagulation*
- Dose and type of fibrinolytic agent**

* Unfractionated heparin is the recommended anticoagulant, in the following regimen:
An i.v. bolus of 60 U/kg (max. 4000 U), followed by
a 48-72 hour infusion 12 U/kg/hr (max. 1000 U/kg/hr)
a PTT monitoring at 3,6,12, 24 hrs after start of treatment (target aPTT: 50-70 sec)

** Fibrin specific agents like rt-PA and TNK-tPA increase the risk of intracranial hemorrhage by a factor 1.5 to 2 when compared to streptokinase. In the case of TNK-tPA, careful attention should be paid to the weight-adjusted dose.

CVA = cerebrovascular accident

TIA = transient ischaemic attack

Table 3 Full dose lytic versus half dose lytic plus glycoprotein-IIb/IIIa blocker - clinical and angiographic findings

	GUSTO V		ASSENT 3		TIMI 14		SPEED		Total *1	
	r-PA	r-PA+Abc	TNK	TNK+Abc	rt-PA	rt-PA+Abc	r-PA	r-PA+Abc	ThX	ThX+Abc
n =	(8260)	(8328)	(4078)	(2016)	(163)	(173)	(108)	(187)	(12609)	(10704)
Mortality %	5.6 (488)	5.9 (468)	5.7 (231)	6.6 (133)	3.1 (5)	4.4 (5)	5.5 (6)	3.7 (7)	5.8 (730)	5.7 (613)
ICH %	0.6 (49)	0.6 (52)	0.9 (37)	0.9 (19)	1.8 (3)	1.2 (2)	0.9 (1)	0.5 (1)	0.7 (90)	0.7 (74)
Major bleeding %	2.3 (190)	4.6 (379)	2.6 (106)	4.3 (87)	4.3 (7)	3.5 (6)	3.7 (4)	8.0 (15)	2.4 (307)	4.5 (487)
Reinfarction %	3.5 (291)	2.3 (190)	3.4 (140)	2.2 (44)	3.1 (5)	n.a.	2.8 (3)	1.6 (3)	3.5 (439)	2.3 (237)
90 min TIMI - 3 %					62	74	47	57		

	Intro AMI		Integriti		Total *2		Total *3	
	rt-PA	rt-PA+Epti	TNK	TNK+Epti	ThX	ThX+Epti	ThX	ThX+GP
n =	(100)	(204)	(118)	(177)	(218)	(381)	(12827)	(11085)
Mortality %	7.0 (7)	4.4 (9)	5.1 (6)	3.6 (6)	6.0 (13)	3.9 (15)	5.8 (743)	5.7 (628)
ICH %	2.0 (2)	2.0 (4)	1.7 (2)	0.6 (1)	1.8 (4)	1.3 (5)	0.7 (94)	0.7 (79)
Major bleeding %	7.0 (7)	10.8 (22)	0.8 (1)	6.8 (12)	3.7 (8)	8.9 (34)	2.5 (315)	4.7 (521)
Reinfarction %	3.0 (3)	4.9 (10)	0 (0)	4.0 (7)	1.4 (3)	4.5 (17)	3.4 (442)	2.3 (254)
90 min TIMI - 3 %	54	58	49*4	62*4				

ThX = thrombolysis; Abc = abciximab; ICH = intracranial haemorrhage; Epti = eptifibatide; GP = glycoprotein IIb-IIIa blocker

*1 = the total of all trials combining abciximab with thrombolysis;

*2 = the total of all trials combining eptifibatide with thrombolysis;

*3 = the total of all trials combining glycoprotein IIb-IIIa blockers with thrombolysis;

*4 = TIMI grade 3 flow percentages at 60 minutes.

n.a = not available

Adjunctive antithrombotic therapy

As stated before, the early and sustained success of fibrinolytic therapy is the result of the balance between forces stimulating lysis and those resulting in (re)occlusion. Adjunctive antithrombotic treatment should therefore be initiated as early as possible, and be continued indefinitely.

Antiplatelet therapy efficacy and safety

– *Aspirin.* Even in the absence of fibrinolytic treatment, the administration of aspirin has been shown to improve survival (6). A simple 35-day intervention with aspirin improved survival with 25 per 1000 treated patients: 10.7% vs. 13.2%. This emphasizes the need to start aspirin in any patient with an acute coronary syndrome. Interestingly, the efficacy of aspirin seems independent of the duration of symptoms (6), in contrast to the benefits of fibrinolytic therapy (1). To induce an immediate effect, the starting dose should be 160 mg or higher, whereas for long-term administration 80-160 mg is sufficient. With regard to safety, quantitative review showed that the irreversible inhibition of cyclo-oxygenase-1 does not result in significant gastro-intestinal bleeding, nor in an increase in intracranial hemorrhage (15).
– *Other antiplatelet agents.* In those patients allergic or intolerant to aspirin, the ADP-receptor antagonist clopidogrel may be considered although only tested in the setting of non ST-elevation acute coronary syndromes (W29). The impact of the routine administration of clopidogrel on top of aspirin in patients treated with fibrinolytic therapy is evaluated in the currently running CLARITY/TIMI-28-trial.

Anticoagulant therapy, efficacy, Table 4

– *Unfractionated heparin.* This agent exerts its effect through potentiation of anti-thrombin III, so called "indirect thrombin inhibition". In the pre-fibrinolytic era, its use has been proven to markedly improve prognosis (16). Yet, since the standardized combined use of aspirin and fibrinolysis few trials re-evaluated its magnitude of benefit (W30).

  Based on pharmacological principles, the use of a bolus of heparin prior to, or concomitant with fibrinolytic therapy would counteract the liberated,

initially clot-entrapped thrombin, and facilitate early reperfusion. From the randomized trials on subcutaneous administration of unfractionated heparin, it was learnt that in-hospital outcome was modestly improved, a benefit that dissipated within three weeks after discontinuation of treatment (W7). For agents such as streptokinase, which results in prolonged fibrin depletion, 48-72 hours of unfractionated heparin is not believed to be of benefit, but placebo-controlled evidence is lacking. The recent findings in the AMI-SK trial suggest that adjunctive anticoagulation is required (W31). As the most successful reperfusion regimen to date (7), the fibrin-specific accelerated rt-PA, has never been tested without heparin, the regimen of newer fibrinolytics always included heparin. This is also based on the observation of a clustering of reinfarctions within the first 10 hours of discontinuation of intravenous heparin (9). This suggests an effect on rethrombosis cq. recurrent ischemic events after fibrinolysis, and forms the rationale of the 48-72 hour infusion. Intravenous heparinization constitutes several drawbacks varying from the use of an infusion pump, hampering mobilization, to the need of regular monitoring as a result of its rather unpredictable and varying plasma levels.

– *Low-molecular-weight heparin.* The introduction of agents like enoxaparin and dalteparin has overcome these problems. They have a better bioavailability, plasma levels are more stable, and monitoring is not necessary. Their impact is believed to be mostly achieved through inhibition of factor Xa and less by inhibition of thrombin activity, and results in similar early patency as unfractionated heparin (W32). The ease of subcutaneous administration also promotes prolonged treatment as performed in the old trials with subcutaneous unfractionated heparin. This reduced in-hospital reinfarction rates during treatment, with a catch-up phenomenon after discontinuation resulting in comparable outcome at 30-days (W33) to 1-year (W34). This supports the impact of continued anticoagulation therapy after fibrinolysis. Interestingly, the AMI-SK trial was the first to properly address the impact of an immediate, prolonged anticoagulation regimen in patients treated with streptokinase. In this placebo-controlled trial, early ST-resolution was significantly better in patients on enoxaparin, as was 5-7 day patency (W31).
– *Direct thrombin inhibitors.* In contrast to heparins, this group of anticoagulants also affects thrombin bound to fibrin and fibrin degradation products. The impact of hirulog was evaluated as compared to unfractionated heparin in the over

17,000 patients HERO-2 trial, addressing ST-elevation myocardial infarction treated with streptokinase. Survival was not affected. In-hospital reinfarction, adjudicated in a blinded fashion, was significantly reduced from 3.6% to 2.8% (W35).

– *Pentasaccharides.* A pentasaccharide is a compound of unfractionated heparin, with the ability to strongly activate the anti-Xa activity of antithrombin-III, affecting the generation of thrombin without any direct effect on thrombin itself. This new agent resulted in similar 90-minute-patency after fibrinolysis as unfractionated heparin. In a secondary analysis, reocclusion was assessed in the subset of patients who did not undergo an intervention. A 5-7 day regimen of this new agent resulted in lower reocclusion rates, as compared to a 48-72 hour treatment with unfractionated heparin: 0.9% vs. 7.0%, respectively (p=0.065) (W36).

In summary, low-molecular-weight heparins are certainly more easily to administer and seem more effective than unfractionated heparin, which may in part be related to their prolonged administration. Whether these or other new agents should be implemented in daily clinical practice also depends on safety aspects.

Anticoagulation, safety, Table 4

– *Unfractionated heparin*. Given the association between the level of anticoagulation and the risk of intracranial hemorrhage after fibrinolysis (9) downward dose-adjustments and more frequent assessment of the aPTT have been introduced (17). This has resulted in reduced rates of intracranial bleeding, without loss of efficacy (W37). The advantage of unfractionated heparin over the newer anticoagulants is the long-term experience in over hundred-thousands of patients. Given the modest impact on survival and reinfarction, safety is an important aspect.
– *Low-molecular-weight heparin.* Whereas enoxaparin seemed an attractive alternative to unfractionated heparin, recent findings call for a more thorough evaluation of the safety of this agent as conjunctive to fibrinolysis. In the setting of non ST-elevation myocardial infarction, enoxaparin proved safe, and seemed to reduce recurrent ischemic events, be it with an administration until discharge as compared to 48-72 hours of unfractionated heparin (W38). The first trial using this enoxaparin regimen with in-hospital fibrinolysis showed increased

overall bleeding rates, but was too small to be conclusive on the risk of intracranial hemorrhage (13). The prehospital moderately sized ASSENT-3 PLUS trial, however, reported a significant increase in the incidence of intracranial hemorrhage in patients on enoxaparin: 2.0 vs 0.9% for unfractionated heparin (W39). The fact that this trial included a higher proportion of older, female patients with a low body-weight revealed this complication. Important other aspects are the lack of a weight-adjusted bolus and the almost doubled half-life of the subcutaneous dosis in elderly patients. The TIMI-25 EXTRACT trial will address the safety of subcutaneous enoxaparin with or without bolus, and in a weight-adjusted dose over the age of 75. In the pending CREATE trial, reviparin, a new low-molecular-weight heparin will be tested.

– *Other anticoagulants.* Given the limited experience with anti-Xa agents, and the higher bleeding rates with the rather expensive direct thrombin inhibitors, these agents are not to be recommended for general implementation. For patients with a heparin induced thrombocytopenia hirudin could serve as an alternative.

Table 4 Angiographic and clinical data on novel anticoagulant strategies as adjunctive to fibrinolytic therapy

		Fibrinolytic agent	New anticoagulant	Unfractionated Heparin	New treatment
Angiographic trials:				*90-minute TIMI-3 flow:*	
HART-2	**(n=400)**	rt-PA	Enoxaparin	48%	53%
PENTALYSE	**(n=333)**	rt-PA	Pentasaccharide	68%	64%
				5-7 day TIMI-3 flow:	
ASSENT-PLUS	**(n=439)**	TNK-tPA	Dalteparin	63%	69%
AMI-SK	**(n=496)**	Streptokinase	Enoxaparin	58% **	70%
Clinical trials, efficacy:				*Death, reinfarction, refractory ischemia:*	
HERO-2	**(n=17,073)**	Streptokinase	Hirulog	13.6%***	12.6%
ASSENT-3	**(n=6,095)**	TNK-tPA	Enoxaparin	15.4% *	11.4%
ASSENT-3 PLUS	**(n=1,639)**	TNK-tPA	Enoxaparin	17.4% *	14.2%
Clinical trials, safety:				*Intracranial hemorrhage:*	
ASSENT-3	**(n=6,095)**	TNK-tPA	Enoxaparin	0.93%	0.88%
ASSENT-3 PLUS	**(n=1,639)**	TNK-tPA	Enoxaparin	0.97%*	2.20%
HERO-2	**(n=17,703)**	Streptokinase	Hirulog	0.40%	0.60%

* significant difference

** placebo control group, significant difference

*** endpoint depicted: death and (adjudicated) reinfarction; P = 0.07.

Prevention of recurrent ischemic events - The (sub)acute and chronic phase -

Irrespective of the initiation of reperfusion therapy, it is of the utmost importance to initiate interventions aimed at early hemodynamic stabilization, prevention of recurrent ischemia and malignant arrhythmias. Moreover, the unstable "hot" plaque should be "cooled off", with agents affecting endothelial function and inflammation as additional treatment to antithrombotic agents (Figure 1).

– *Nitrates.* Due to its vasodilatation these agents are recommended for the first 24-48 hours in patients with persistent ischemia, hypertension, heart failure and large anterior infarction (W40,W41).
– *Beta-blockers.* Given the unfavorable prognostic impact of recurrent ischemia (W42), beta-blockers are a key intervention in the setting of myocardial infarction. In addition, its anti-hypertensive and, in particular, anti-arrhythmic properties are thought to form a major contribution to its beneficial effects on survival, as well as its beneficial effect on the incidence of cardiac rupture. Although the majority of evidence stems from the pre-fibrinolytic era (18,W43) this does not restrain its applicability in the current era of reperfusion therapy. Specifically in patients with restored patency the salvaged myocardium remains at renewed risk of ischemia, especially in the early phase, which was underscored in the TIMI-IIb trial. Early initiation, i.e. within 2 hours, significantly reduced the combined (secondary) endpoint of reinfarction and recurrent ischemia in the first week as compared to patients in whom beta-blockers were initiated after this first week (W44). With respect to the choice of agent, cardioselective beta-blockers like atenolol and metoprolol are to be preferred over agents like propranolol, in order to avoid or reduce beta-2 related side effects. Importantly, randomized data on the use of cardioselective agents in patients with reactive airway disease only resulted in a limited decrease in FEV1 not associated with adverse respiratory effects (W45). Moreover, observational data in over 200,000 patients suggest that patients believed to have a relative contra-indication, i.e. diabetes, asthma etc., benefit from beta-blockers without clinically important side effects (W46). Thus, beta-blockers should be initiated as early as possible and deserve a central role in the (sub)acute phase and follow-up treatment of all patients with acute myocardial infarction, including those with left ventricular dysfunction, also in the era of reperfusion therapy (W47). Importantly, intolerable side effects

can be directly antagonized, in contrast to those of calcium channel blockers.

– *Calcium channel blockers.* Short-acting agents from the dihydropyridine class like nifedipine are contra-indicated in the setting of myocardial infarction, given their negative effects as a result of reflex sympathetic stimulation, tachycardia and hypotension (19,W48). Long-acting agents, and the other calcium antagonists like diltiazem and verapamil have failed to improve survival (W49,W50,W51,W52,W53). For the latter agents, reduction of recurrent ischemic events has been demonstrated in a selected patient population, without left ventricular dysfunction (W49,W50). Therefore, its use should primarily be restricted to co-administration with a beta-blocker in the case of recurrent ischemia.
– *ACE-inhibitors.* Patients with particular benefit are those with large infarcts, not only those with clinical signs of heart failure (W54,W55), but also in the asymptomatic patient with a reduced left ventricular function (W55,W56). As much of the survival advantage is realized in the first 48 hours, early initiation of oral treatment is indicated (20,W40,W41,W57,W58). With the emerging evidence that various subgroups of patients benefit from treatment, a six-week treatment period for all patients after infarction can certainly be considered (20). In the case of heart failure and reduced left ventricular function, angiotensin-blockers can be used as an alternative, but also in addition to ACE-inhibitors to reduce cardiovascular, though not all-cause, mortality (W59).
- *Statins.* The need for long-term use of statins is undisputed (W60,W61,W62). With respect to the additional impact of early initiation, no trials for ST-elevation myocardial infarction are available. Data from the MIRACL study suggest a reduced incidence of recurrent ischemic events with early treatment after a non ST-elevation acute coronary syndrome (W63).
– *Additional antithrombotic treatment.* Although a prolonged combined antithrombotic regimen of aspirin and (oral) anticoagulation has proven of additional benefit (5), the need of a good infrastructure of oral anticoagulation control has hampered implementation in daily care. With the successful initial data on the oral direct thrombin inhibitor ximelagatran on top of aspirin, this problem may be solved, which facilitates future comparisons with dual antiplatelet regimens (W64). The beneficial impact of the standard addition of clopidogrel has been proven in non ST-elevation acute coronary syndromes, and is currently under investigation in the large ST-elevation CCS2 trial. Therefore,

the majority of patients after ST-elevation myocardial infarction only receives treatment with aspirin at discharge, which should be used indefinitely.

Recommendations

In view of the fact that many patients with an ST-elevation myocardial infarction will not be treated by primary angioplasty in lack of a proper infrastructure, optimal pharmacological treatment is warranted. Importantly, time to initiation of treatment is a crucial element, a factor that can be positively influenced by early, preferably prehospital initiation of pharmacological reperfusion therapy. When primarily adopting a pharmacological approach to reperfusion therapy in ST-elevation myocardial infarction, an individually tailored approach with respect to the choice of a fibrin-specific or non-fibrin specific agent is a prerequisite, balancing the respective risks and benefits, which also holds true for the decision of rescue angioplasty. Aspirin, anticoagulation and early initiation of beta-blockade form the key triade of adjunctive treatment in the acute phase. The use of calcium channel blockers should be reserved to co-treatment with a beta-blocker, and only agents from the non-dihydropyridine class, like diltiazem, can be considered as an alternative to beta-blocker treatment in the case of clinically proven intolerance. In the subgroups of patients with a reduced left ventricular function, or clinical signs of heart failure ACE-inhibitors are indicated, and a six-week treatment period can be considered in all patients with an acute coronary syndrome. Finally, in order to prevent recurrent ischemic events and malignant arrhythmias and to stabilize the “hot” plaque, the continued use of aspirin and beta-blockers is recommended, complemented by long-term statin therapy.

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CHAPTER 4

Influence of early/prehospital thrombolysis on mortality and event-free survival

The Myocardial Triage and Intervention Randomized Trial

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Abstract

Background: The Myocardial Infarction Triage and Intervention Trial of prehospital versus hospital administration of thromoblytic therapy markedly reduced hospital treatment times and the 2 groups had similar outcomes. However, patients treated < 70 minutes from symptom onset had better short-term outcomes. The purpose of this study was to determine the long-term influence of very early thrombolytic treatment for acute myocardial infarction.

Methods and Results: A total of 360 patients were followed for vital status and cardiac-related hospital admissions over a period of 34 ± 16 months. Patients enrolled in the trial had symptoms for ≤ 6 hours, ST-segment elevation on the prehospital electrocardiogram, and no risk factors for serious bleeding. They received aspirin and recombinant tissue plasminogen activator either before or after hospital arrival. Primary end points in this study included long-term survival and survival free of readmission to the hospital for myocardial infarction, revascularization, angina, or congestive heart failure. Two-year survival was 89% for prehospital- en 91% for hospital-treated patients (p=0.46). Event-free survival at 2 years was 56% and 64% for prehospital- and hospital-treated patients, respectively (p=0.42). In patients treated < 70 minutes from symptom onset, 2-year survival was 98%, and it was 88% for those treated later (p=0.12). Two-year event-free survival was 65% for patients treated early and 59% for patients treated later (p=0.80).

Conclusions: In this trial, poorer long-term survival was associated with advanced age, history of congestive heart failure, and coronary artery bypass surgery performed before the index hospitalization, but not with time to treatment.

Introduction

Thrombolytic therapy has been proven to reduce early mortality and to improve 1-year survival rates in patients with acute myocardial infarction. (1-7) The greatest mortality reduction is shown in patients who receive treatment within the first 1 to 2 hours after symptom onset. (3,5,6,8) In several studies that have determined the components of treatment delay, patient decision time and hospital treatment times each could account for $\geq$ 1 hour. Prehospital initiation of thrombolytic therapy might therefore provide the opportunity to treat a large proportion of patients within the first 2 hours of symptom onset.

Two trials of prehospital thrombolytic therapy demonstrated significant reductions in time to treatment, although mortality in the prehospital and hospital groups was not significantly different (12,13).

In the Myocardial Infarction Triage and Intervention (MITI) prehospital trial, time to treatment was reduced by 33 minutes in the prehospital group. In addition, patients treated < 70 minutes from symptom onset had lower mortality, smaller infarct size, and improved left ventricular function (13).

Over the years, several studies reporting the long-term influence of thrombolytic therapy have been published (14,15,16). The purpose of the current study was to determine whether the benefits of very early treatment were sustained in the years after discharge from the hospital.

Methods

Patient population

All patients who called 911 and had chest pain were evaluated by the 15 paramedic units in the Seattle metropolitan area. Using a checklist with inclusion and exclusion criteria, paramedics gathered information on the patients' clinical presentations. This information enabled hospital-based physicians to determine whether the patients were candidates for thrombolytic therapy. Patients were excluded from participating in the trial for the following reasons: (1) chest pain > 6 hours from symptom onset, (2) age > 75 years, or (3) the presence of complicating illnesses that were considered to be contraindications for prehospital thrombolytic therapy. Detailed information on the study protocol and criteria for patient selection have been published (11,13).

Briefly, a 12-lead prehospital electrocardiogram was obtained in the subset of patients who satisfied the criteria for enrollment. The final decision to randomize the patient was made by a physician in the emergency department of 1 of 6 paramedic base hospitals. Paramedics used a standard verbal consent to enrol patients into the study. After enrollment, patients were randomized to receive aspirin and recombinant tissue plasminogen activator either before or after hospital arrival. Intravenous sodium heparin was administered to both patient groups at the time of hospital arrival. After hospital discharge, 289 patients underwent radionuclide measurements of infarct size and left ventricular ejection fraction.

Follow-up

To determine survival status and the need for readmission to the hospital for cardiac reasons, mail questionnaires were sent to patients annually. Patients were queried concerning hospital admissions for the following reasons: (1) angiography, (2) coronary angioplasty, (3) coronary artery bypass surgery, (4) congestive heart failure, (5) chest pain, or (6) subsequent myocardial infarction. In addition to the mail questionnaires, hospital admission logs were screened for cardiac-related admissions. Information about procedures and admission and discharge diagnoses was also recorded. Telephone contact with patients or surviving relatives often enabled us to complete missing information. Finally, the National Death Index was used to ascertain vital status for patients lost to follow-up.

Statistical methods

The primary end points of this study were survival and event-free survival, defined as survival free of myocardial infarction, or hospitalization for angina, congestive heart failure, or revascularization. Survival analyses included deaths from all causes. Survival curves for all groups were obtained according to the method of Kaplan and Meier (17). The log rank test was used to determine whether survival and event-free survival were different according to randomization group and time to treatment, dichotomized by a 70-minute cutpoint. Stepwise Cox regression analysis was used to identify factors related to long-term survival; variables were included in the model if the p value for inclusion was < 0.05. To compare the numbers of cardiac-related hospital admissions, we calculated the average number of events per patient per follow-up year. Baseline characteristics and clinical outcomes were compared by the chi-square test for discrete variables and the t test for continuous variables.

Results

Of all 360 patients, 175 were randomized to receive prehospital-initiated thrombolytic therapy, and the other 185 were allocated to thrombolytic treatment after hospital arrival. Baseline characteristics of these patients have been described (13). Cardiac histories and hemodynamic findings did not differ significantly between the groups, and baseline electrocardiographic findings were also similar: Anterior infarction occurred in 39% (p=0.99) and inferior infarction in 58% (p=0.99) of both groups. Patients in the hospital group were slightly older than their counterparts (59 ± 10 years in the hospital group vs. 57 ± 10 years in the prehospital group; p = 0.04). Time from symptom onset to treatment differed significantly; the median time to treatment for the prehospital group was 77 minutes (56 and 101; 25th and 75th percentiles), and it was 110 minutes (85 and 140; 25th and 75th percentiles) for the hospital group (p < 0.0001). Overall, 336 patients received thrombolytic therapy in either the prehospital or the hospital setting; 24 did not receive thrombolytic treatment for varying reasons (13). In nearly 25% (82 of 336) of the patients receiving thrombolytic therapy, time from symptom onset to treatment was < 70 minutes. Most were treated later; 254 patients received thrombolytic therapy between 70 minutes and 3 hours of symptom onset.

The baseline characateristics of patients treated early (< 70 minutes) and of those treated later were similar. Patients in the early group were slightly younger, although this difference was not statistically significant (56 ± 10 years in the early-treated patients vs 58 ± 10 years in the later-treated patients; p = 0.051) Time to treatment showed a distinct difference: The median time to treatment was 55 minutes (49 and 63; 25th and 75th percentiles) for the early-treated patients compared with 104.5 minutes (85 and 141; 25th and 75th percentiles) for those who were treated later.

Prehospital vs In-Hospital Thrombolysis

In the first year of follow-up, 31 patients died; information on cardiac-related events was available for 97% of patients. With the National Death Index and returned follow-up letters, it was possible to ascertain vital status for all patients. Figure 1 shows cumulative survival curves for the prehospital and hospital groups. There was no significant difference in long-term survival between the two groups; 2-year survival was 89% for prehospital-treated patients and 91% for those treated in the hospital setting (p= 0.46). Event-free survival also did not differ according to

randomization group (Figure 2). Two years after enrolment, event-free survival was 56% and 64% in the prehospital and hospital groups, respectively (p=0.42).
To determine whether patients differed in the number of cardiac-related events, we calculated event rates for both groups (Table 1). The prehospital group showed a slightly lower number of cardiac-related admissions (p=0.28). Overall, there was a difference of 68 cardiac-related events per 1,000 patients per year (Table 1). Hospital readmission rates at 1 and 2 years of follow-up were also determined. For the prehospital group, 31% and 36% of patients were rehospitalized at 1 and 2 years, respectively. In the hospital group, 25% of patients were readmitted at 1 year and 31% at 2 years (p=0.65).

Effect of time to treatment

During the first year of follow-up, 28 of 336 patients who received thrombolytic therapy died. Information on cardiac-related events was available for 96% of surviving patients. Figure 3 shows the long-term survival for the group that was treated very early versus the group that received thrombolytic agents $\geq$ 70 minutes from symptom onset. Unadjusted survival in the early-treatment group appeared to be improved, but the difference was not statistically significant, because the survival curves crossed after 3 years. Two-year survival was 98% for the early-treated patients and 88% for those who received thrombolytics later (p=0.12).
Figure 4 shows that there was no significant difference in event-free survival between the very early and the later-treated group. Event-free survival at 2 years was 65% for the early group and 59% for the later group (p=0.80). Event rates were similar in the 2 groups (Table 2). Readmission rates at 1 and 2 years of follow-up were 30% and 33%, respectively, for the early-treated patients and 27% and 33% for those treated later. These differences were not statistically significant (p=0.74).
To identify factors that were related to long-term survival, we performed Cox multivariate regression analysis in 329 patients with complete information. Advanced age, a history of heart failure, and bypass surgery performed before the index hospitalization were associated with decreased survival. After adjustment for these variables, treatment < 70 minutes from symptom onset was not associated with survival (p=0.30). In addition, time to treatment measured as a continuous variable was not predictive of long-term survival (p=0.84).

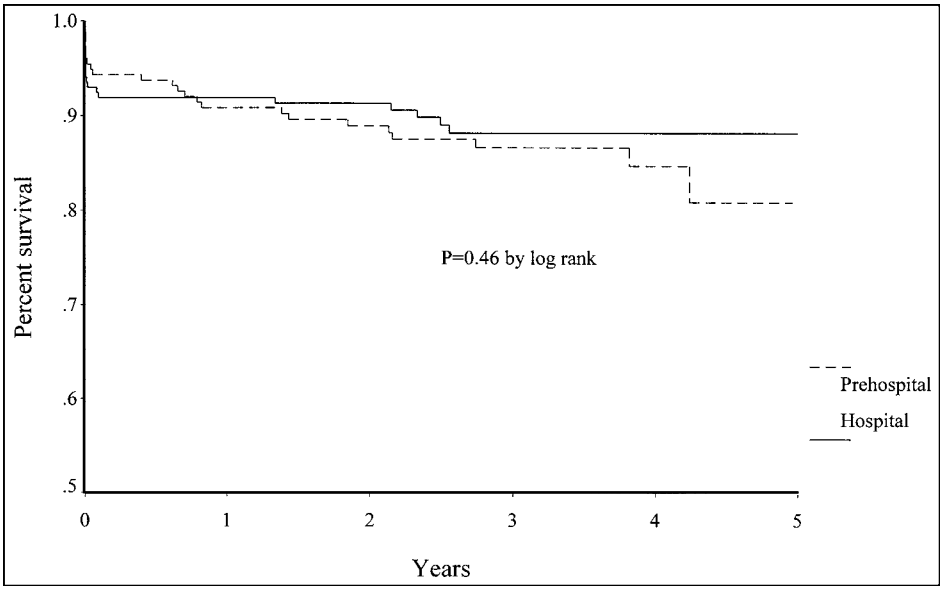

Figure 1: Long-term survival for patients after prehospital and in-hospital thrombolysis

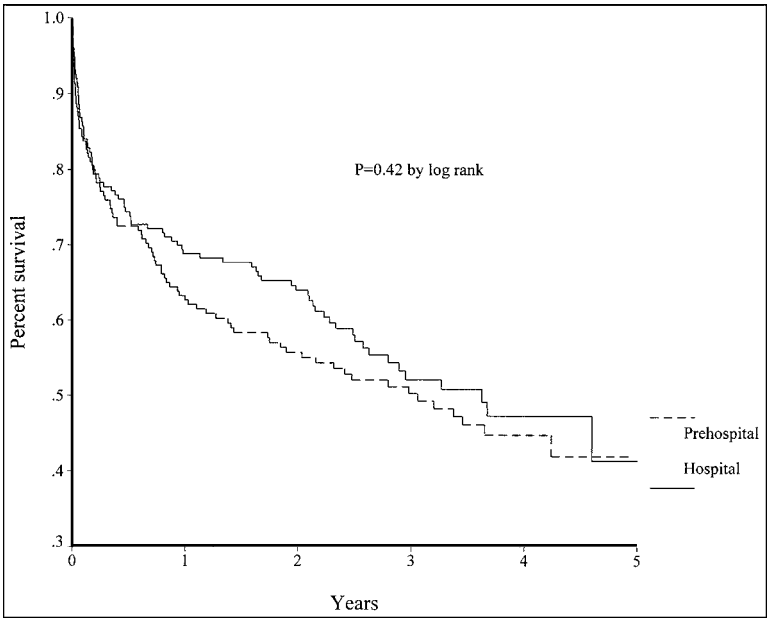

Figure 2: Long-term event-free survival for patients after prehospital and in-hospital thrombolysis

Table 1 Observed cardiac-related events for both randomized groups

	Number of Events		Number of events/ 100 patients/year		
Event	**Prehospital (n = 175)**	**Hospital (n = 185)**	**Prehospital (n = 175)**	**Hospital (n = 185)**	**p Value**
Angiography	54	70	11.5	13.8	0.37
Angioplasty	34	43	7.0	8.5	0.45
Bypass Surgery	20	20	4.1	4.0	0.90
Congestive Heart Failure	12	13	2.6	2.5	0.94
Myocardial infarction	22	21	4.3	4.3	0.98
Recurrent ischemia	24	40	4.9	7.9	0.11
Total	166	207	34.2	41.0	0.28

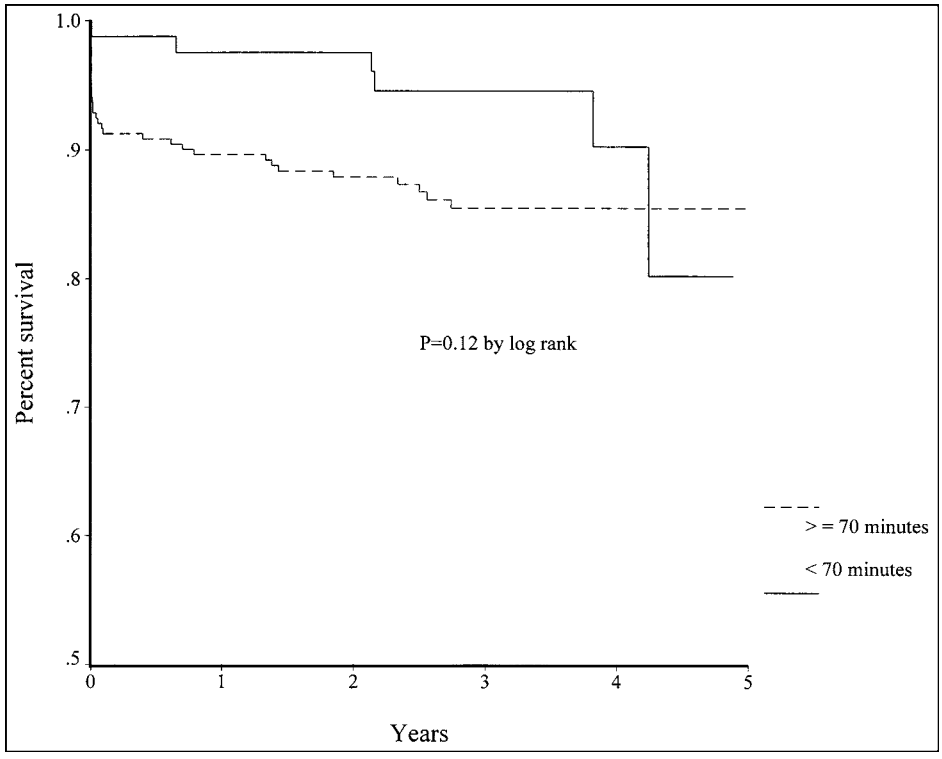

Figure 3: Long-term survival for patients treated within and later than 70 minutes after symptom onset

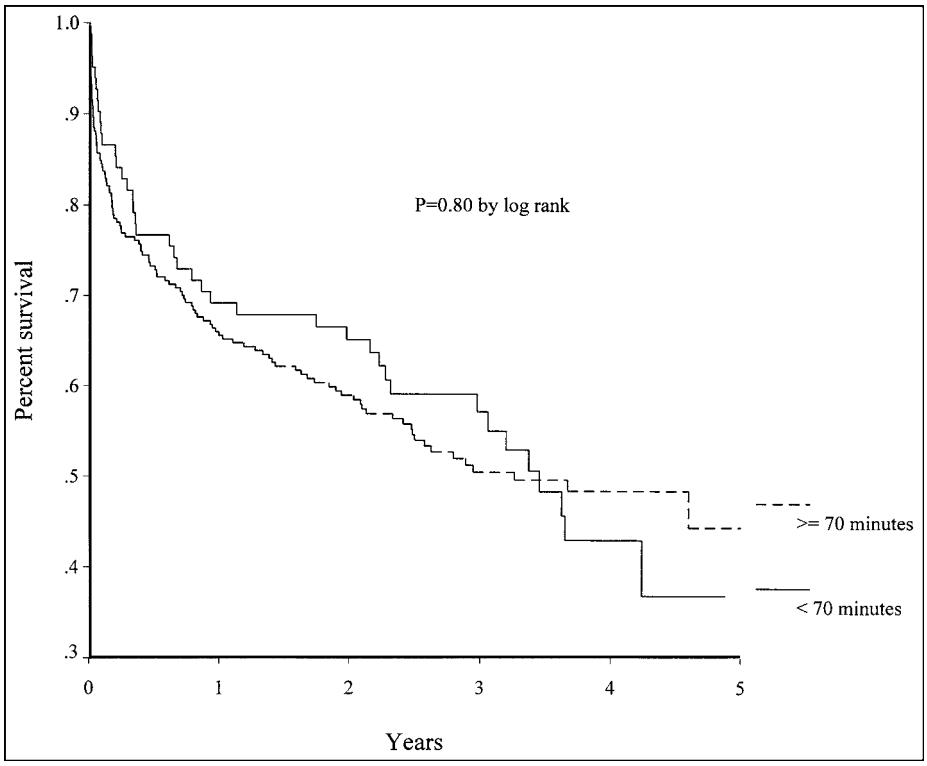

Figure 4: Long-term event-free survival for patients treated within and later than 70 minutes after symptom onset

Table 2 Observed cardiac-related events for patients treated very early and those treated later

	Number of Events		Number of events/ 100 patients/year		
Event	**< 70 min (n = 82)**	**≥ 70 min (n = 254)**	**< 70 min (n = 82)**	**≥ 70 min (n = 254)**	**p Value**
Angiography	27	89	11.0	13.1	0.45
Angioplasty	22	46	9.0	6.8	0.35
Bypass Surgery	9	29	3.7	4.3	0.69
Congestive Heart Failure	4	19	1.6	2.8	0.38
Myocardial infarction	8	35	3.3	5.1	0.18
Recurrent ischemia	11	49	4.5	7.2	0.18
Total	81	267	33.0	39.2	0.35

Discussion

Time to treatment is an important predictor of hospital mortality (3,8,13). The earlier thrombolytic treatment is initiated, the more myocardium is saved and the better the clinical outcome. According to this hypothesis, outcome would be best in patients treated very early. We conducted this follow-up study to assess the long-term influence of very early initiation of thrombolytic therapy.

There was a trend toward improved long-term survival after very early thrombolysis. This benefit resulted primarily from a much more favorable in-hospital mortality rate for patients treated very early. Moreover, readmission rates and event-free survival were not influenced by a substantial reduction in time to treatment. Therefore, despite the major impact of early treatment on short-term mortality, the influence on long-term clinical outcome was less impressive. The benefits of very early treatment are immediate; with the passage of time, other factors, including age and gender, as well as the use of aspirin, beta blockers, risk factor reduction, or revascularization procedures, become pre-eminent for all patients.

Survival curves for the prehospital- and hospital-treated patients were similar. These findings may have been influenced by the unanticipated reduction of 40 minutes in hospital treatment times in this study (13). Consequently, prehospital initiation of thrombolytic therapy resulted in a reduction in time to treatment of only 33 minutes, instead of the expected time of $\geq$ 1 hour (13).

This, combined with the conservative selection criteria and the relatively low patient numbers, might have prevented the difference between treatment groups that was expected. In the analysis of early treatment, the earlier reported 30-day survival benefit for patients treated < 70 minutes from symptom onset resulted in markedly improved survival in this group. This gain was caused primarily by a lower number of in-hospital deaths for the early-treated patients. Considering the entire follow-up period, the observed difference between curves was not statistically significant ($p=0.12$). In addition, results from Cox regression analysis indicated that early treatment was not associated with long-term survival. These findings do not suggest that very early treatment exerts an additional salutary effect that was realized in the first month after treatment.

Event-free survival was not influenced by a reduction in time to treatment. Readmission rates and the event rates also did not differ significantly. The slightly higher event-free percentages in the very early-treated group were caused by fewer

deaths in this group and not by a difference in hospital admissions for cardiac events. These findings do not support the hypothesis that early treatment would result in improved overall cardiac status and thus fewer subsequent admissions. A Dutch study has suggested that freedom from reocclusion does result in improved long-term event-free survival (18).

Follow-up in the MITI prehospital thrombolysis trial demonstrated that short- and long-term clinical outcomes were similar for prehospital- and hospital-treated patients. Thirty-day survival was improved with very early thrombolytic therapy, but very early treatment did not decrease either subsequent survival or the number of cardiac events after hospital discharge.

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CHAPTER 5

Adverse long-term effects of reocclusion after coronary thrombolysis

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Abstract

Objectives: This study sought to assess the long-term clinical consequences of reocclusion after coronary thrombolysis.

Background: After acute myocardial infarction successfully treated with thrombolysis, reocclusion occurs in ~30% of patients and leads to poorer in-hospital outcome. However, the long-term effects of reocclusion are unknown.

Methods: Three hundred patients with no history of coronary surgery and with a patent infarct-related artery at coronary angiography within 48 h after thrombolysis were enrolled in the Antithrombotics in the Prevention of Reocclusion in COronary Thrombolysis (APRICOT) trial. At a mean (±SD) of 77 ± 23 days after thrombolysis, 248 patients (87%) underwent follow-up angiography. Reocclusion was observed in 71 (29%) of 248 patients. To compare outcome between 71 patients with and 177 without reocclusion an analysis of event-free survival, defined as a clinical course without death, reinfarction and revascularization, was performed.

Results: Over a 3-year follow-up period, event-free survival was significantly better in patients without reocclusion: At 1 year it was 63% for patients with and 83% for those without reocclusion ($p<0.001$). In the first year, two or more cardiac-related events occurred in 24% of patients with and 6% of those without reocclusion ($p<0.001$). Patients with reocclusion had a markedly higher reinfarction and revascularization rate. At 1 year the reinfarction rate was 23% for patients with and 5% for those without reocclusion ($p<0.001$).

Conclusions: This analysis shows the adverse influence of reocclusion on long-term clinical outcome in relation to reinfarction and need for revascularization. To further optimize prognosis after thrombolysis, prevention of reocclusion should become a main priority. Future research should focus on the criteria and timing of elective revascularization procedures in the prevention of coronary reocclusion.

Introduction

In the past decade, thrombolytic therapy has become the cornerstone of treatment for acute transmural myocardial infarction. In 80% of all treated patients, recanalization of the infarct-related artery is eventually achieved. (1) However, several studies (2-8) have demonstrated that reocclusion occurs in 5% to 30% of patients after successful thrombolysis. Reocclusion has proved to be associated with an adverse short-term clinical outcome (3) and impaired residual left ventricular function (3,9), the most important prognostic factor after myocardial infarction after thrombolysis (10). The benefit of thrombolytic therapy – improvement of both short- and long-term survival – could therefore be optimized by the prevention of reocclusion. Routine invasive strategies after thrombolysis have not been shown to improve clinical outcome (11). There have been several studies (2-8) specifically addressing coronary reocclusion and the intermediate-term effects of oral antithrombotic therapy on reocclusion. These studies may provide insight into the long-term effects of reocclusion after coronary thrombolysis.

Several trials (12-14) have been conducted to determine long-term survival after thrombolytic therapy. To our knowledge, this report is the first follow-up study to assess the effects of reocclusion on long-term clinical outcome. The data are derived from the Antithrombotics in the Prevention of Reocclusion in COronary Thrombolysis (APRICOT) trial (2).

Methods

Study protocol

A detailed description of the APRICOT study protocol and criteria used to select patients has previously been published (2). In brief, 300 patients ≤ 70 years old with no history of coronary surgery were enrolled between August 15, 1987 and June 30, 1991. They presented with chest pain lasting > 30 min and < 4 h combined with a minimum of 0.2mV of ST segment elevation in two contiguous electrocardiographic (ECG) leads. They received thrombolytic therapy with either streptokinase or anistreplase followed by a fixed dose of intravenous heparin (20,000 U/24 h). Downward dose adjustments were made only when the activated partial thromboplastin time exceeded 2.5 times baseline values. Standard coronary care treatment was given (15). Within 48 h after the start of thrombolytic treatment, coronary angiography showed grade 1 to 3 stenosis of the infarct-related artery according to the criteria defined by the European Cooperative Study Group (16). European Cooperative Study Group grades 1 to 3 are identical to Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow. Sixteen patients were retrospectively judged to have an occluded infarct-related artery and were not included in the study (Fig. 1).

All 284 patients with a patent infarct-related artery were randomized to treatment with 325 mg of aspirin daily, coumadin (international normalized ratio 2.8 to 4.0) or placebo. Infarct-related artery status at 3 months was the primary end point of the APRICOT trial. Revascularization was performed for clinical reasons only. Thirty-six patients did not undergo follow-up angiography because of refusal (n = 28), coronary bypass surgery (n = 6) or death (n = 2) (Fig. 1). Reocclusion was defined as a grade 4 to 5 stenosis (16) and corresponds to TIMI flow grades 0 to 2. The culprit lesions of patients undergoing angioplasty before the scheduled second angiography were analyzed in the catheterization laboratory immediately before the angioplasty procedure. On the basis of results of the second angiography, two groups of patients were defined:

1. 71 patients with reocclusion; and
2. 177 without reocclusion.

Follow-up

Patients that participated in the APRICOT trial were screened for cardiac-related events over a 3-year follow-up period. Medical files were used to study hospital admissions for the following reasons: coronary angioplasty, coronary bypass surgery and reinfarction. In addition, survival status of all enrolled patients was assessed. Municipal registries and telephone contact with the patient, general practitioner or relatives enabled us to complete missing information.

Clinical end points

Outcome between groups was compared according to vessel status at the second angiography, and clinical information since the day of randomization was used. The primary end point of the analysis was event-free survival. An event-free follow-up was defined as a clinical course without death, reinfarction or readmission for coronary angioplasty or coronary bypass surgery. Criteria for recurrent myocardial infarction were chest pain accompanied by typical ECG changes combined with an increase in creatine kinase levels higher than twice the upper normal limit.

Statistics

Baseline characteristics are expressed as mean value ± SD and were compared by the Student's t test. Whenever appropriate, the chi-square test was used for other comparisons between groups. Event-free survival curves were obtained as described by Kaplan and Meier (17). To determine the statistical significance of the difference between curves, the log-rank test was used. A p value < 0.05 was considered statistically significant.

Results

Follow-up

Of the 284 patients participating in the APRICOT trial, 248 (87%) had a second coronary angiography performed at a mean of 77 ± 23 days after thrombolysis (Fig. 1). Patients without angiographic follow-up more often had a history of myocardial infarction (17% vs. 6%, $p < 0.025$), were slightly older (60 ± 7 vs. 56 ± 9 years, $p < 0.01$) and were more often female (31% vs. 17%, $p < 0.05$) (2). The 248 patients with both a first and a second angiography formed the present study group. Follow-up data were collected for a median of 31 months (25^{th} to 75^{th} percentile, 19 to 46 months) starting on the day of randomization. No patient was lost to follow-up. In the first follow-up year six patients died. Information on 238 (98%) of the surviving 242 patients after > 1 year of follow-up was available.

Table 1 shows the baseline characteristics of patients with and without reocclusion. No statistical differences were observed.

Clinical outcome

Figure 2 shows event-free survival in patients with and without reocclusion over a 3-year follow-up period. In the reocclusion group, the majority of all events occurred in the first 3 months. In this short period of time, the event-free survival rate decreased to 68% for patients with reocclusion compared with 92% for those without reocclusion. There was a significant ($p < 0.001$) overall difference in the event-free survival curves, with most of the difference occurring within the first weeks. At 1 year these percentages were 63% and 83%, respectively ($p < 0.001$). Over the entire follow-up period, 19 patients (27%) with and 16 patients (9%) without reocclusion had a reinfarction. Reinfarction occurred in the same area as the index infarction, exept in one patient. Proportionally, the reocclusion group experienced three times as many reinfarctions (Table 2). Data are expressed as event counts rather than event rates because of the decreasing follow-up percentage after the first year of follow-up.

In the first year of follow-up the incidence of cardiac-related events was 59% for patients with and 24% for those without reocclusion ($p < 0.001$). These rates were similar over 3 years: 75% for the former and 33% for the latter. Patients without reocclusion experienced 39 cardiac-related events in the first year of follow-up. Forty-four percent of events occurred within 3 months after randomization, in

contrast to 74% of all observed events in patients with reocclusion ($p < 0.03$). At 1 year of follow-up, a clinical course with two or more cardiac-related events was seen in 24% of patients with, compared to 6% of patients without reocclusion ($p < 0.001$). Over the entire follow-up period, multiple events occurred in 22 patients (31%) with and 15 (9%) without reocclusion.

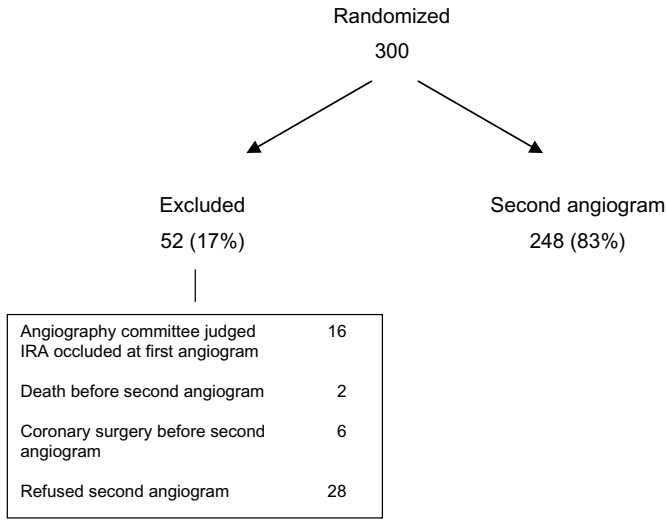

Figure 1: Reasons for not undergoing follow-up coronary angiography after 3 months. IRA= infarct-related artery

Table 1 Baseline characteristics in patients with and without reocclusion

	No reocclusion n = 177	**Reocclusion n = 71**
Male (%)	81%	87%
Age (years)	56 ± 9	57 ± 9
Angina pectoris		
< 4 wk	52 (29%)	25 (35%)
≥ 4 wk	33 (19%)	15 (21%)
Previous myocardial infarction	11 (6%)	4 (6%)
Time of symptoms (thrombolysis) (h)	2.0 ± 1.0	2.0 ± 1.1
Peak creatine kinase (U/liter)	1,545 ± 1,509	1,567 ± 1,419
Study medication		
Aspirin	70 (40%)	23 (23%)
Coumadin	57 (32%)	24 (34%)
Placebo	50 (28%)	24 (34%)
Infarct-related artery:		
LAD	71 (40%)	34 (48%)
LCX	28 (16%)	11 (16%)
RCA	78 (44%)	26 (37%)
One-vessel disease	106 (60%)	36 (51%)
Two-vessel disease	49 (28%)	24 (34%)
Three-vessel disease	22 (12%)	11 (16%)
Ejection fraction (%)	51 ± 10	52 ± 13
No. of pts	120	52
End-systolic volume (ml)	76 ± 29	73 ± 31
No. of pts	97	46
End-diastolic volume (ml)	152 ± 43	152 ± 39
No. of pts	97	46

Unless otherwise indicated, data presented are mean value ± SD or number (%) of patients (pts).
LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery;
RCA = right coronary artery.

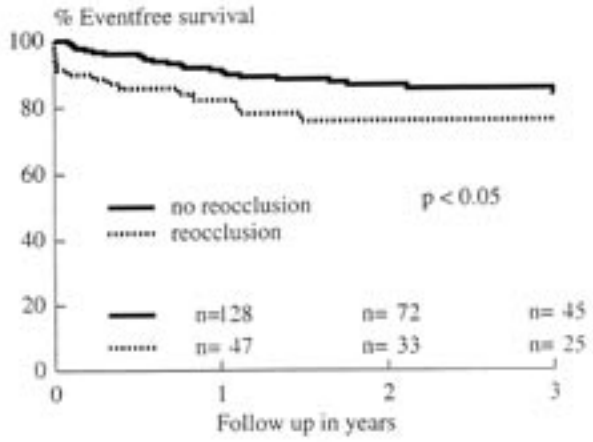

Figure 2: Event-free survival (defined as a clinical course without death, reinfarction or revascularization) in patients with and without reocclusion. The follow-up period starts at first coronary angiography (within 48 hours after successful thrombolysis)

Table 2 Clinical events over 3-year follow-up in patients with and without reocclusion

	Before 2nd Angio	2nd Angio to 1st yr	2nd yr	3rd yr	Total
No. of patients with reocclusion at risk (n=71)	71	48	45	27	71
Death	2	1	2	1	6 (9%)
Reinfarction	5	1	2	1	19 (27%)
PTCA	12	6	3	0	21 (30%)
CABG	2	3	2	0	7 (10%)
Total	31	11	9	2	53 (75%)
No. of patients without reocclusion (n=177)	177	163	147	94	177
Death	0	3	3	0	6 (3%)
Reinfarction	3	5	6	2	16 (9%)
PTCA	12	9	3	0	24 (14%)
CABG	3	4	4	1	12 (7%)
Total	18	21	16	3	58 (33%)

Data presented are number or number (%) of patients (pts). Angio = Angiography; CABG = coronary artery bypass grafting; PTCA = percuteneous transluminal coronary angioplasty.

Discussion

Reocclusion and event-free survival

To our knowledge, this is the first study to demonstrate the sustained adverse influence of reocclusion on clinical outcome. The first months after successful thrombolysis appear to be of major importance: ~60% of all cardiac-related events in the reocclusion group occurred within 3 months after thrombolytic therapy. Although the mortality rate was low, a result of the study design (2), there was a marked difference in event-free survival in favour of patients without reocclusion, due to the relatively high rate of reinfarction and angioplasty in patients with reocclusion.

Long-term survival after myocardial infarction is primarily predicted by the functional status of the left ventricle (18). Reocclusion is associated with impaired recovery of left ventricular function (3,9). These findings strongly suggest that mortality would have been higher if selection criteria had not been as strict as in the present study. The 1-year mortality rate for the study group was 2.4%. Even over a 3-year follow-up period, only 12 (5%) of 248 patients died. Three-year survival rates reported by long-term survival trials of thrombolysis vary from 84% to 87% (12,14). Because of the low mortality profile, the difference in event-free survival might even be slightly underestimated.

Reocclusion and reinfarction

Reinfarction occurs more frequently in patients with than without reocclusion. Our data are in accordance with earlier findings (3) showing that most recurrent ischemic events occur within the first days after thrombolytic therapy. The majority of the reocclusions (78%) are not associated with clinically apparent reinfarction. During this period and thereafter, reocclusion is likely to occur asymptomatically because of the development of collateral channels (19). Only two of the 15 reinfarctions observed in the first 3 months did not occur within 10 days. Overall, 84% of the reinfarctions in the reocclusion group occurred within 3 months after enrollment. In contrast, only 20% of the reinfarctions in patients without reocclusion occurred in the 3-month period. Therefore, in this group, 80% of the reinfarctions occurred later in the first year and in the second and third follow-up year. These reinfarctions are most likely to be related to the ongoing atherosclerotic process, whereas the early reinfarctions most likely result from rethrombosis after thrombolytic therapy (12).

Reocclusion and need for revascularization

Over the entire follow-up period, revascularizations represented the majority of cardiac-related events. It should be noted that these procedures were performed for clinical, not angiographic, reasons only. In the reocclusion group, ~50% of all angioplasty procedures were performed before the second angiography. The information obtained at angiographic follow-up may have caused the physician to perform more revascularizations than usual. However, the consequences for the pattern of the event-free survival curves are negligible because the period leading up to the second angiography is of greater clinical importance.

Reocclusion and multiple events

Reocclusion has proved to be associated with a higher incidence of cardiac-related events and hospital admissions. Only 15 (9%) of the 177 patients without reocclusion had two or more events compared with 22 (31%) of 71 with reocclusion. Therefore, nearly 33% of patients with reocclusion experienced multiple events. This finding, combined with the fact that 37 patients with reocclusion had no events, indicates that some patients with reocclusion have a higher risk for a complicated clinical course than others.

Effects of thrombolytic therapy on long-term improvement

The results of the present study emphasize the clinical importance of an initially and persistently patent infarct-related artery in comparison with an initially open but reoccluded artery. An earlier long-term analysis (20) of the prognostic effects of patency included only one angiographic observation performed 1 month after thrombolysis and also identified patency as an important prognostic factor, which proved to be independent of left ventricular function.

To optimize the results of thrombolytic therapy, a combination of two approaches might be successful:

1. The reocclusion rate should be reduced as much as possible. New antithrombotic drugs, such as hirudin and hirulog (6,21), may better prevent reocclusion. Identification of patients with a high risk for reocclusion would also be of major importance. So far, clinical variables have failed to determine predictors of reocclusion (22).
2. Patients with reocclusion might benefit from elective angioplasty within a few weeks after myocardial infarction, when coronary angioplasty can safely

be performed, especially if collateral supply is sufficient. Late recanalization may prevent ventricular dilation (23,24). This ventricular enlargement is a compensatory mechanism to restore stroke volume at the expense of an increased preload and afterload to the left ventricle, which may stimulate further dilatation (9,25). It has been demonstrated that ventricular enlargement occurs more frequently with an occluded than with a patent infarct-related artery (9,26,27) and that reperfusion can prevent dilation (28).

One could argue whether all patients of the reocclusion group would have benefited from a recanalization procedure. More than 50% of patients with reocclusion had no events over a 3-year follow-up period; however, asymptomatic reocclusion might have occurred in some of them. An option would be to perform coronary angioplasty in a prespecified subgroup. Our data show that new cardiac-related events are most likely to occur in patients with an event in the first 3 months. Twenty-two new events occurred after angiographic follow-up: 11 occurred in patients who had already had 1 event.

In the APRICOT trial (2), a conservative strategy was intended: Revascularizations were performed only for reasons of recurrent ischemia not responsive to medical anti-ischemic treatment. The advantage of elective angioplasty would be that ventricular enlargement would be less extensive than with angioplasty performed at the time of symptoms. These options should be investigated further, because the optimal benefits of thrombolytic therapy have not yet been attained.

Study limitations

One limitation of the present study design is that only patients who survived the acute phase and, in addition, were fit enough to undergo catheterization within 48 h, were eligible to enter the study. Furthermore, only patients who had a patent infarct-related artery at first angiography and underwent follow-up angiography were included in this analysis. This selection bias certainly contributed to the low mortality rate observed and may have influenced the number of observed events. Another restriction concerns the exclusion of patients with coronary bypass surgery before the second angiography. Finally, only patients $\leq$ 70 years of age participated in the trial, which may also have contributed to an underestimation of the incidence of cardiac-related events after successful thrombolysis. Despite the aforementioned restrictions, the number of revascularizations might have been lower if a second

angiography had not been performed. Generally, symptoms of recurrent ischemia not responding to anti-ischemic treatment would be an indication to perform revascularization. In the present trial, the information obtained at follow-up angiography may have led the physician to follow a less conservative treatment strategy.

Conclusions

The results of the present study demonstrate that reocclusion after successful thrombolysis for acute myocardial infarction is associated with a less favorable long-term clinical course. Reocclusion results in a relatively high rate of reinfarction and angioplasty procedures during the first 3 months, drastically affecting event-free survival. The observed effect on clinical outcome remains significant over a 3-year follow-up period. These findings underscore that both the prevention, and, possibly, adequate treatment of reocclusion should become the main priorities of thrombolytic therapy for myocardial infarction. Future research might focus on the timing, criteria and results of elective revascularization procedures.

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CHAPTER 6

Antiplatelet therapy and progression of coronary artery disease: a placebo-controlled trial with angiographic and clinical follow-up after myocardial infarction

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Submitted

Abstract

Objectives: To determine whether anti-platelet therapy influences coronary disease progression in non-infarct arteries.

Background: After ST-elevation myocardial infarction (MI), anti-platelet therapy reduces subsequent cardiac events, which are often attributed to recurrent thrombosis and occlusion of the infarct-related artery. Little data is available regarding the impact on non-infarct artery coronary disease progression.

Methods and Results: Quantitative coronary angiography (QCA) was undertaken on paired cine-angiograms of 154 patients from fibrinolytic trials who had a patent infarct-related artery at 3-4 weeks following ST-elevation MI and who were randomized to either continue the daily combination of 50-mg aspirin and 400-mg dipyridamole or to matching placebo. Follow-up angiography was scheduled at one year and data suitable for analysis was available on non-infarct arteries in 149 patients. Progression was prespecified as an 0.40 mm change in MLD.

On a per patient basis, the change in MLD was 0.00 mm (95% confidence interval [CI]: -0.05 mm to 0.05 mm) in the aspirin/dipyridamole group (n=76) and was 0.01 mm (95%CI: -0.04 mm to 0.06 mm) in the placebo group (n=73). The difference between these groups in the changes in MLD was not significant (-0.02 mm; 95%CI: -0.09 – 0.05); neither were there significant differences in mean luminal diameter (0.02 mm; 95%CI: -0.06 – 0.11) and diameter stenosis (1.3%; 95%CI: -0.2 – 2.8). Per segment comparisons between aspirin/dipyridamole (n=732) and placebo (n=704) did not show a treatment effect on any of the QCA-parameters. The proportions of patients with progression were 68% and 64%, respectively (p=0.7). Progression did not independently predict clinical outcome (median follow-up 99 months).

Conclusion: In this randomized placebo-controlled follow-up trial after ST-elevation myocardial infarction, the combination of aspirin and dipyridamole did not affect non-infarct artery disease progression over 1 year. Progression occurred in two thirds of patients, but did not predict long-term outcome.

Introduction

Anti-platelet therapy has been shown to reduce early and late mortality and reinfarction after ST-elevation myocardial infarction [MI] (1). Half of these reinfarctions occur within 48 hours of fibrinolysis for ST-elevation MI and are often associated with reocclusion of the infarct-related artery [IRA] (2,3). Aspirin has been associated with a 50% reduction in in-hospital reocclusion of the IRA after MI (4). However, in patients who survive the acute phase, anti-platelet therapy has not been shown to reduce late reocclusion up to one year (5,6).

Nevertheless, a large meta-analysis demonstrated that aspirin still confers clinical benefit when initiated a month or more after an acute coronary syndrome, albeit with a less pronounced relative risk reduction (1). This suggests that aspirin may have an effect on thrombotic occlusions on plaques related to the non-infarct arteries, as the likelihood of infarct artery related events decreases over time. The mechanism of benefit of long-term aspirin therapy shown in the Anti-Thrombotic Trialists' Collaboration (1) may in part be due to an influence on the occurrence of thrombosis in non-infarct arteries.

The clinical manifestations of coronary thrombosis may only represent the "tip of the iceberg" of all thrombotic processes in the coronary arteries. In the absence of clinical ischemic events, serial angiographic studies have demonstrated that progression is a phasic rather than a linear process (7,8). It is postulated that clinically silent repeated plaque rupture and fissuring with mural thrombus formation and subsequent reorganization may lead to progression of coronary artery disease (9). Moreover, at the time of an acute event, non-occlusive thrombus formation has also been demonstrated in non-infarct arteries in up to 20% of patients (10). Given the inhibitory effect on platelet aggregation, aspirin might influence this more subtle, often subclinical process of coronary artery disease progression. To examine the influence of aspirin, in combination with dipyridamole, on progression in non-infarct arteries in the year after ST-elevation MI, we assessed changes in paired non-culprit coronary artery segments by quantitative coronary angiography (QCA) .

Methods

Study patients

The study group comprised consecutive consenting patients with ST-elevation MI, who presented within 4 hours of the onset of ischaemic chest pain who were enrolled in two trials of fibrinolytic therapies from 1984-1988 (11,12), and who had thrombolysis in myocardial infarction (TIMI) grade 2 or 3 flow in the IRA at 3 to 4 weeks. These patients were then randomized to continue an oral combination of 50-mg aspirin and 400-mg dipyridamole daily (Asasantin, Boehringer Ingelheim) or to receive matching placebo until follow-up angiography, which was scheduled at one year (6). A conservative approach to revascularization was adopted (6) and over the year only 5% of patients underwent coronary artery bypass grafting or coronary angioplasty.

Coronary angiography

Sublingual nitroglycerin was given prior to coronary angiography, which was performed in the standard manner by the femoral approach with hand injection. Cine-angiography was recorded at 25 frames per second (6,13). Left ventriculography and calculation of end-systolic volume index were performed as previously described (14). Blood flow in the IRA was assessed as previously described; patency was defined as TIMI flow grade 2 or 3 (6). The culprit stenosis in the IRA was defined as the stenosis, with angiographic thrombus, or the one that best correlated with the regional wall and/or electrocardiographic abnormalities (13). Coronary artery stenoses, the number of diseased vessels and the coronary segments were determined according to the Coronary Artery Surgery Study (CASS) criteria (15).

Quantitative Coronary Angiography

Quantitative coronary angiography (QCA) analysis was performed on 154 paired cine-angiograms with identical coronary artery views. Suitable coronary segments were assessed irrespective of stenosis severity by an experienced QCA angiographer (BJW) at our angiographic laboratory. The analysis of each pair of angiograms was performed in one session to avoid time-related changes, and was undertaken blinded to treatment allocation and the order of films. Analysis of cine-frames was performed in end diastole, free of superimposed structures and foreshortening. QCA

analyses were done using the Cardiovascular Measurement System (CMS-MEDIS Medical Imaging Systems) and the 1-cm grid was used for calibration, although in some patients a non-tapering portion of an angiographic catheter was used. QCA analysis included the minimal luminal diameter (MLD; mm), mean luminal diameter (mm), diameter stenosis (%) and reference diameter (mm) for each segment. The reproducibility of the QCA analysis in our laboratory has previously been reported (16). For MLD the standard deviation for repeat measurement was 0.17 mm from pairs of angiograms at an interval of 2 months. We prospectively defined a change of ≥ 0.40 mm in MLD as progression of a coronary lesion over a one-year period for consistency with previous reports (17).

Angiographic endpoint

The angiographic endpoints were the one-year changes in MLD, mean luminal diameter and diameter stenosis on a per patient basis in non-IRA segments. The changes in these QCA-measures between angiograms (angiogram 2 - angiogram 1) were compared between the aspirin/dipyridamole and placebo groups. To calculate the average changes on a per patient basis, the differences in the respective QCA-parameters observed in the paired coronary segments were added for each patient individually, and subsequently divided by the number of contributing segments.

Patients with a new occlusion or at least one lesion worsening ≥ 0.40 mm in MLD in the non-infarct artery segments were defined as showing progression (progressors) and all other patients were defined as non-progressors. Patients with new lesion formation had at least one segment with a diameter stenosis ≤ 20% at baseline, worsening ≥ 0.40 mm in MLD to a ≥ 20% diameter stenosis at follow-up angiography. Semi-quantitative analysis defining the proportion of progressors and non-progressors was also used to compare randomized treatment allocations. To assess the aspirin/dipyridamole therapy at the level of individual coronary segments, analyses on a per segment basis were performed.

Progression and long-term clinical follow-up

Late follow-up was performed by recording hospitalizations, recall to the outpatient clinic, by the family doctor, by telephone or by mail. Reinfarction was defined as an admission for prolonged ischaemic chest pain and a creatine kinase level > 2 times the upper limit of the reference range and/or development of new Q-waves. All events were verified by source documents.

The long-term clinical impact of progression was studied using the semi-quantitative dichotomous definition. Additionally, the long-term clinical impact of progression was assessed with progression 1) as a continuous variable and 2) divided in quartiles of the 1-year changes in minimal luminal diameter.

Statistical analyses

Normally distributed continuous variables are expressed as means and standard deviations and these were compared using a paired T-test or an independent T-test for within group differences and between group differences, respectively. Continuous variables not normally distributed are expressed as medians and interquartile ranges (IQR). These were compared using non-parametric tests. Proportions were compared by chi-square and Fisher's exact tests. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Multivariable predictors of clinical outcome were identified using the Cox proportional-hazards regression model, using forward and backward logistic regression analysis. Included were variables that significantly differed, or tended to differ between progressors and non-progressors ($p < 0.10$), and variables associated with clinical outcome ($p < 0.10$). Irrespective of their corresponding p-values in univariate analyses, age, previous myocardial infarction and end-systolic volume index (18) were chosen to be included. A two-sided $p < 0.05$ for all hypothesis tests was considered to be significant.

Results

Study population

Of 215 patients with TIMI grade 2 or 3 flow (patency) in the IRA at a median of 25 days (IQR: 21 - 32), ten patients died and 51 patients did not undergo follow-up angiography because of refusal (Figure 1). There were no differences in baseline characteristics and clinical outcomes between the 51 patients with a single angiogram and the 154 patients with paired angiograms. Clinical and angiographic baseline characteristics of the treatment and placebo group are shown in Table 1. Thirteen patients had a non-fatal reinfarction before the planned follow-up angiogram, seven patients in the aspirin/dipyridamole group and six patients in the placebo group. Nine revascularizations were performed between angiograms, five in the treatment group (3 CABG and 2 PCI) and four in the placebo group (1 CABG and 3 PCI).

Angiographic changes over 1 year: impact of anti-platelet therapy

Per patient analysis. Data suitable for analysis on non-infarct arteries was available in 149 patients (Figure 1). The QCA values according to treatment on a per patient basis are shown in Table 2 and Figure 2.

Patients in the aspirin/dipyridamole group did not have a significantly different change in QCA-parameters over one year as compared to the placebo group. The respective differences in the 1-year changes were: 1) MLD -0.02 mm (95%CI: -0.09 – 0.05); 2) mean luminal diameter 0.02 mm (95%CI: -0.06 – 0.11); 3) diameter stenosis 1.3% (95%CI: -0.2 – 2.8)

Semi-quantitative analysis. No treatment effect could be demonstrated on semi-quantitative analysis: 68% of patients allocated to aspirin/dipyridamole therapy and 64% in the placebo group were progressors ($p = 0.7$). Two patients, one in each group, had a silent occlusion of an initially patent non-infarct artery at follow-up angiography, both patients had reocclusion of the IRA as well. New lesion formation was present in 17% of the patients in the aspirin/dipyridamole group and 22% of the patients in the placebo group ($p = 0.5$).

Per segment analysis. A total of 1436 paired non-IRA coronary segments were available for analysis, 732 in the aspirin/dipyridamole group and 704 in the placebo group; baseline characteristics on a per segment basis were similar between the treatment groups. QCA analysis by treatment allocation on a per segment basis

showed no differences between the aspirin/dipyridamole and placebo group in any QCA parameter (Table 3). However, there were significant within group differences over 1 year in the mean luminal diameter, diameter stenosis and the reference diameter in the aspirin/dipyridamole group (all with $p < 0.01$). In the placebo group, the within group differences were significant for mean luminal diameter and reference diameter (both $p < 0.05$).

In segments with a baseline stenosis of ≥ 50%, both groups (aspirin/dypiridamole and placebo) showed a significant increase in MLD at one year, but no treatment effect was observed (0.18 mm vs. 0.20 mm; $p = 0.7$, respectively). Analysis of various other angiographic subgroups for changes in MLD (LAD vs. non-LAD, proximal vs. mid vs. distal segments) did not show a treatment effect either.

Late prognostic significance of progression

There were 99 patients with angiographic progression and 50 patients without progression. The clinical and demographic baseline characteristics did not differ. At first angiography significantly wider baseline minimal and mean luminal diameters were found for progressors as compared to non-progressors (2.03 mm ± 0.34 vs. 1.77 mm ± 0.33 and 2.72 mm ± 0.39 vs. 2.44 mm ± 0.35, respectively).

The 149 patients were followed for a median of 99 months (IQR, 86 - 113) after follow-up angiography. Cardiac death occurred in 20 patients (13%), cardiac death and myocardial infarction occurred in 31 patients (20%).

The long-term survival free from the combined endpoint of cardiac death and myocardial infarction in progressors compared to non-progressors is shown in Figure 3. Progressors had a survival rate free from cardiac death and reinfarction of 79% as compared to 71% for non-progressors ($p = 0.3$).

In the case progression was assessed based on changes in all coronary arteries, including the IRA, progression was seen in 87% of patients (aspirin/dipyridamole 84% vs. placebo 89%, $p = 0.4$). Event-free survival did not differ either between progressors and non-progressors (76% vs. 77%, respectively, $p = 0.9$).

A multivariable model with the following variables was used to assess a potential independent association between progression and clinical outcome (see Methods): age, previous myocardial infarction, end-systolic volume index, vessel disease and the average minimal luminal diameter and mean luminal diameter per patient at baseline angiography. Cox regression identified one independent predictor of long-term cardiac mortality and reinfarction: end-systolic volume index, Hazard

Ratio (HR): 1.02 (95%CI: 1.00 - 1.05, p = 0.04). Multivessel disease tended to be an independent predictor, HR: 1.96 (95%CI: 0.94 - 4.06, p = 0.07). Progression as a dichotomous variable was not independently associated with long-term cardiac mortality nor with the combined endpoint cardiac death and reinfarction. When entered as a continuous variable, or in quartiles, the 1-year changes in minimal luminal diameter were not associated with long-term outcome either.

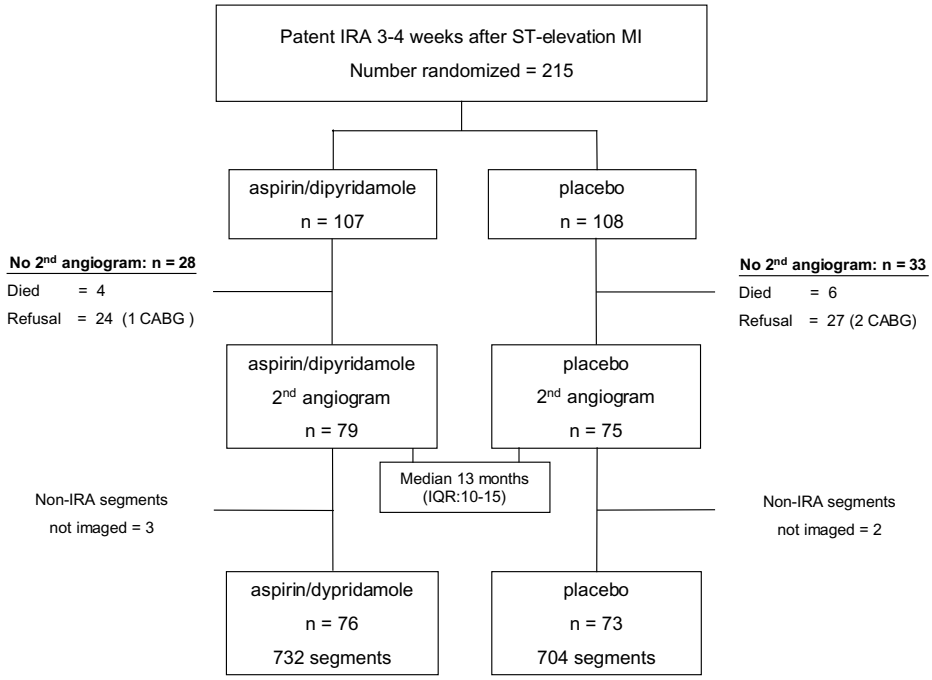


Figure 1: Flow chart showing the number of patients and segments suitable for QCA-analysis.
IRA = infarct-related artery; MI = myocardial infarction; IQR = Interquartile range.

Table 1 Clinical and Angiographic baseline Characteristics: Aspirin/Dipyridamole versus Placebo

	Aspirin/Dipyridamole n = 79	**Placebo n = 75**
Age (years)	55 ± 9	56 ± 8
Male	82%	76%
Smoking	48%	48%
Diabetes	10%	5%
hypertension	30%	25%
Total Cholesterol (mmol/l)	6.3 ± 1.3	6.3 ± 1.3
History of MI	6%	8%
CTFC (of IRA) (IQR)	26 (18 – 41)	31 (20 – 48)
CK-max (U/l) (IQR)	2300 (1033 – 3258)	2196 (1700 – 3525)
Infarct-related artery :		
LAD	33%	43%
RCA	56%	43%
LCX	11%	14%
Vessel disease (CASS) :		
0 vessel	27%	32%
1 vessel	48%	45%
2 vessels	14%	12%
3 vessels	11%	11%

Data are presented as a percentage for discrete variables (%), as mean ± SD for continuous variables and as median (interquartile range) for continuous data not normally distributed. MI = myocardial infarction; CTFC = corrected TIMI frame count; IRA = infarct-related artery; CK = creatine kinase; LAD = left anterior descending artery; RCA = right coronary artery; LCX = left circumflex coronary artery; CASS = coronary artery surgery study.

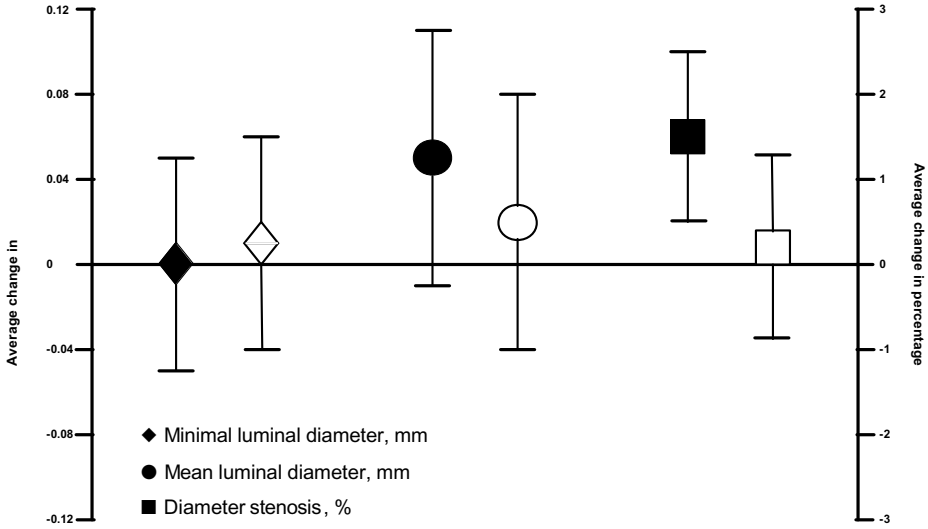


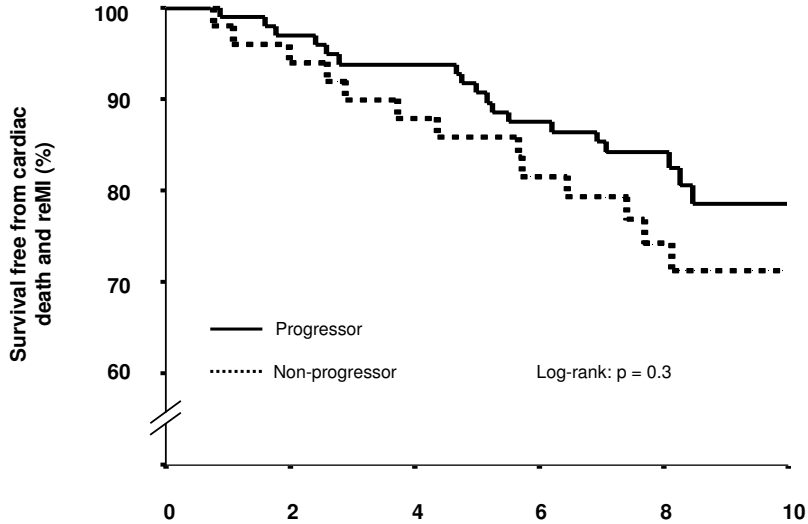
Figure 2: Mean changes with 95% CIs in quantitative coronary angiographic parameters of non-infarct artery segments at one-year follow-up angiography on a per patient basis: aspirin/dipyridamole versus placebo.

black = Aspirin/Dipyridamole
white = Placebo

Table 2 Quantitative coronary angiography measurements: Per patient analysis of non-infarct arteries

	Aspirin/ Dipyridamole n = 76	Placebo n = 73	p Value
Minimal Luminal Diameter, mm			
Baseline	1.92 (1.85 – 1.99)	1.97 (1.88 – 2.06)	0.4
Follow–up	1.91 (1.84 – 1.98)	1.98 (1.89 – 2.07)	0.2
Change	-0.00 (-0.05 – 0.05)	0.01 (-0.04 – 0.06)	0.6
Mean Luminal Diameter, mm			
Baseline	2.60 (2.51 – 2.69)	2.65 (2.55 – 2.75)	0.4
Follow–up	2.65 (2.57 – 2.73)	2.67 (2.57 – 2.77)	0.7
Change	0.05 (-0.01 – 0.11)	0.02 (-0.04 – 0.08)	0.5
Diameter Stenosis, %			
Baseline	33.7 (32.3 – 35.1)	33.5 (32.0 – 35.0)	0.8
Follow–up	35.2 (33.7 – 36.7)	33.7 (32.0 – 35.4)	0.2
Change	1.5 (0.5 – 2.5)	0.2 (-0.9 – 1.3)	0.08
Reference Diameter, mm			
Baseline	2.81 (2.72 – 2.90)	2.87 (2.75 – 2.99)	0.4
Follow–up	2.86 (2.77 – 2.95)	2.89 (2.78 – 3.00)	0.6
Change	0.05 (0.00 – 0.10)	0.02 (-0.04 – 0.08)	0.6
Progression	68%	64%	0.7
New lesion	17%	22%	0.5

Data are presented as the per patient mean of QCA parameters of non-infarct artery segments, between brackets the 95% Confidence Interval.



Patients at risk							
Progressor	(n)	99	94	90	83	53	13
Non-progressor	(n)	50	47	43	37	26	6

Figure 3: Long-term survival free from cardiac death and non-fatal myocardial infarction: progressors versus non-progressors in non-infarct related arteries.
ReMI = recurrent myocardial infarction

Table 3 Quantitative coronary angiography measurements: Per segment analysis of non-infarct arteries

	Aspirin/ Dipyridamole n = 732	Placebo n = 704	p Value
Minimal Luminal Diameter, mm			
Baseline	1.90 (1.83 – 1.97)	1.94 (1.86 – 2.02)	0.5
Follow-up	1.92 (1.85 – 1.99)	1.97 (1.89 – 2.05)	0.4
Change	0.02 (-0.01 – 0.05)	0.03 (-0.01 – 0.07)	0.6
Mean Luminal Diameter, mm			
Baseline	2.58 (2.51 – 2.65)	2.62 (2.54 – 2.70)	0.5
Follow-up	2.64 (2.57 – 2.71)	2.65 (2.57– 2.73)	0.8
Change	0.06 (0.03 – 0.09)	0.03 (0.00 – 0.06)	0.2
Diameter Stenosis, %			
Baseline	33.5 (32.5 – 34.5)	33.3 (32.2 – 34.4)	0.8
Follow-up	34.7 (33.7 – 35.7)	33.6 (32.5 – 34.7)	0.1
Change	1.2 (0.4 – 1.8)	0.2 (-0.7 – 1.1)	0.1
Reference Diameter, mm			
Baseline	2.78 (2.70 – 2.86)	2.83 (2.75 – 2.91)	0.4
Follow-up	2.83 (2.75 – 2.91)	2.87 (2.79 – 2.95)	0.6
Change	0.06 (0.03 – 0.09)	0.04 (0.00 – 0.08)	0.5

Data are presented as the average QCA parameters of non-infarct artery segments, between brackets the 95% Confidence Interval. A/D = aspirin/dipyridamole; P = placebo.

Discussion

To our knowledge, this is the first randomized placebo-controlled angiographic follow-up study to examine the influence of anti-platelet therapy on the progression of coronary artery disease as assessed by QCA in non-infarct artery segments in the first year after ST-elevation MI. Progression of coronary artery disease, observed in two thirds of our patients, was not significantly affected by a combined anti-platelet regimen of aspirin and dipyridamole. Neither QCA analysis on a per segment basis, nor a semi-quantitative analysis demonstrated a significant treatment effect. New lesion formation was less common in patients randomized to anti-platelet therapy, 17% vs. 22%, but this difference was not significant. The increase in the diameter stenosis in patients allocated to combined anti-platelet therapy was unexpected, and may be related to vasodilatation caused by dipyridamole, or neurohumoral effects on coronary arteries after myocardial infarction (19).

Effect of anti-platelet therapy on clinical and angiographic outcomes

The clinical benefit of aspirin after myocardial infarction is undisputed (1). Most early reinfarctions are attributed to infarct artery reocclusion and the 50% reduction in in-hospital reocclusion seems a likely explanation for at least part of the mechanism of early benefit with aspirin therapy (4). However, despite its proven long-term clinical efficacy, anti-platelet therapy initiated 24 hours to 3 weeks after acute myocardial infarction has no statistically significant effect on reocclusion at 3-months and 1-year respectively (5,6). The initiation of aspirin approximately 2-6 months after an acute event confers a clinical benefit (1), albeit less pronounced than when therapy is initiated immediately. This suggests the possibility that aspirin may have an effect on thrombotic events not associated with plaque rupture in the IRA, as the likelihood of infarct artery related events decreases over time.

In our analysis of angiographic progression of coronary artery disease in non-infarct arteries, no treatment effect of aspirin/dipyridamole could be demonstrated. In spite of the relatively short follow-up duration, the small changes in QCA measurements in our study were of the same order of magnitude as those shown in trials of lipid modifying therapies, referring to patients with stable coronary artery disease and with longer time intervals between angiograms (17). Moreover, our analysis of post-MI patients showed higher rates of patients with at least one progressing lesion compared to the studies of clinically stable patients. The observed rates of

progression in the present analysis were comparable to the single angiographic trial of lipid lowering therapy after MI (20). Thus, in spite of a high-risk population for progression no treatment effect of aspirin/dipyridamole could be substantiated. The data for the current analysis stem from the time period 1984-1988 and although dietary advice was routinely given, statins and other lipid modifying drugs were not commonly used in this time period. Confouding of our results by lipid modifying drugs is therefore unlikely.

Lack of angiographic benefit of anti-platelet therapy

There are several potential explanations for the lack of a demonstrable effect of anti-platelet therapy on coronary artery disease progression in our study. Firstly, coronary angiography may not be sensitive enough to discern subtle changes in coronary atheroma progression/regression. Intravascular ultrasound (IVUS) is currently the method more frequently used to assess disease progression, because in addition to the coronary lumen, the arterial wall with different structural entities can be visualized. Serial IVUS analysis has demonstrated that improvement of the lipid profile is associated with a reduction of atheroma volume expansion, probably due to growth retardation of the lipid core (21).

With respect to anti-platelet therapy, IVUS studies on coronary disease progression are lacking. As of to date, one other angiographic follow-up study has been reported, in preliminary form (22). The available clinical, angiographic and animal studies have suggested that the mechanism of benefit of aspirin therapy mainly concerns an anti-thrombotic effect: it reduces the incidence of (sub) acute recurrent thrombotic events and has been shown to prevent (sub) total coronary (re) thrombosis in experimental and angiographic models. With respect to the usually sub-clinical, non-occlusive process of mural thrombosis, animal studies suggest an incomplete inhibitory effect of aspirin in this milieu (23) and it has been postulated that to decrease the superficial deposition of platelets, anti-thrombin therapy is required to counteract the strong thrombin effect of aggregates of platelets (23).

These observations of an incomplete anti-platelet effect on mural platelet aggregation, provide mechanistic support for the lack of a demonstrable effect on the process of coronary progression. Occlusions in non-infarct arteries were too infrequent to address a potential anti-thrombotic effect. It is uncertain whether aspirin has effects on plaques other than inhibition of platelet aggregation. It is possible that the anti-inflammatory properties of aspirin could have a role in

plaque stability, albeit at a higher and more frequent dosage as the lowest effective antithrombotic dose regulary used in daily clinical practice.

Although the combination of aspirin 50-mg and dipyridamole 400-mg which we used in this study has not been investigated extensively, a recent meta-analysis showed no dose-related difference in the risk reduction conferred by aspirin (1). Moreover, a combined anti-platelet regimen was found to result in risk reductions in clinical endpoints at least as large as those occurring with aspirin alone (1). In the CABADAS trial, a subgroup of patients with saphenous vein grafts and small calibre distal arteries randomized to the same combined anti-platelet regimen as in the current study had a lower 1-year occlusion rate as compared to patients randomized to aspirin alone (24).

Correlation of angiographic observations and clinical outcome

Angiographic progression has been reported as a predictor of future cardiac events (25). However there is no uniformity in the definition of progression, with one study that correlated per patient average decrease in MLD as a continuous variable with outcome (26), whereas another described progression in a semi-quantitative manner (25), with a dichotomous comparison. In this study we used both definitions of progression, including a prespecified absolute change in MLD of 0.40 mm to assess this endpoint. Although progression occurred in the majority of our patients we did not find that progression was a predictor of future ischemic events. In lack of a generally accepted definition of progression, of which the clinical impact has proved reproducible, caution should be taken to make inferences from angiographic trials to the potential impact in daily clinical practice.

This statement is supported by the fact that clinical trials of ACE-inhibitors and poly-unsaturated fatty acids have unequivocally demonstrated a reduction in MI in patients with stable angina (27) and of sudden death after myocardial infarction (28), whereas in angiographic follow-up trials these agents did not modify progression of atherosclerosis (29,30).

Another example concerns hormone replacement therapy which did not affect coronary disease progression, but proved prothrombotic in large scale clinical trials (31,32). Part of this problem may be related to the fact that the timing of the second angiography influences the chances of detecting clinical recurrent thrombosis, the most outspoken form of coronary artery disease progression. If in the case of recurrent ischemic events immediate follow-up angiography would have been

performed, progression due to coronary thrombosis might have been detected more easily.

Limitations

Angiography only yields information about the coronary lumen, and vessel tortuosity, overlap of structures and effects of lumen shape may confound the assessment of progression. In the present analysis, a conservative revascularization strategy was adopted and a systematic elective follow-up angiography was performed at one year. Consequently, a clinically mandated, earlier performed angiography in the setting of a readmission for a recurrent acute coronary syndrome was not frequently performed and not used as angiographic follow-up endpoint. With 1-year angiography representing a snapshot in time, progression may not have been detected in patients with intercurrent clinical thrombosis before the scheduled repeat angiography.

Conclusion

In this randomized placebo-controlled angiographic follow-up trial in patients with a patent IRA 3-4 weeks after ST-elevation myocardial infarction, the combination of aspirin and dipyridamole did not affect one-year coronary artery disease progression in non-culprit artery segments as assessed by quantitative angiography. Progression, though present in two thirds of patients, was not validated as a surrogate endpoint for long-term clinical events.

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CHAPTER 7

Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction

Results of the Antithrombotics in the Prevention of Reocclusion In COronary Thrombolysis (APRICOT)-2 Trial

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Abstract

Background: Despite the use of aspirin, reocclusion of the infarct-related artery occurs in ~ 30% of patients within the first year after successful fibrinolysis, with impaired clinical outcome. This study sought to assess the impact of a prolonged anticoagulation regimen as adjunctive to aspirin in the prevention of reocclusion and recurrent ischemic events after fibrinolysis for ST-elevation myocardial infarction.

Methods and Results: At coronary angiography < 48 hours after fibrinolytic therapy, 308 patients on aspirin and intravenous heparin had a patent infarct-related artery (Thrombolysis In Myocardial Infarction [TIMI] grade 3 flow). They were randomly assigned to standard heparinization and continuation of aspirin alone or to a 3-month combination of aspirin with moderate-intensity coumarin, including continued heparinization until a target international normalized ratio (INR) of 2.0 to 3.0. Angiographic and clinical follow-up were assessed at 3 months.

Median INR was 2.6 (25^{th} to 75^{th} percentiles 2.1 to 3.1). Reocclusion (TIMI grade 2 flow) was observed in 15% of patients on aspirin and coumarin compared with 28% in those receiving aspirin alone (relative risk [RR], 0.55; 95% CI 0.33 to 0.90; $p < 0.02$). TIMI grade 0 to 1 flow rates were 9% and 20%, respectively (RR 0.46; 95%CI 0.24-0.89; $p < 0.02$). Survival rates free from reinfarction and revascularization were 86% and 66%, respectively ($p < 0.01$). Bleeding (TIMI major and minor) was infrequent: 5% versus 3% (p = ns).

Conclusion: As adjunctive to aspirin, a 3-month-regimen of moderate-intensity coumarin, including heparinization until the target INR is reached, markedly reduces reocclusion and recurrent events after successful fibrinolysis. This conceptual study provides a mechanistic rationale to further investigate the role of prolonged anticoagulation after fibrinolytic therapy.

Introduction

With the introduction of fibrinolytic therapy, survival after ST-elevation myocardial infarction has been shown to largely depend on early restoration of coronary patency (1).

Recurrent ischemic events are often attributed to reocclusion of the infarct-related artery (2,3). Reocclusion is a time-dependent phenomenon (4), which is seen in ~ 10% of patients at the time of discharge (5), with an incidence of up to ~ 30% in the first year, despite the use of aspirin (6,7). Previous studies have demonstrated a 2-fold increased risk of mortality in the case of early reocclusion after successful thrombolysis (2) and a higher risk of reinfarction and recurrent ischemic events in both the short term and the long term (3). Even in the absence of clinical reinfarction, reocclusion has been shown to preclude recovery of left ventricular function (8), the most important determinant of prognosis after myocardial infarction. Prevention of reocclusion is therefore warranted.

Although aspirin has become the standard antithrombotic therapy, oral anticoagulation has also been shown markedly effective in coronary artery disease (9). In patients with non ST-elevation acute coronary syndromes (9-11), a combined regimen of anti-platelet and anticoagulation therapy seemed promising.

It was therefore hypothesized that outcome after ST-elevation myocardial infarction could be improved by a prolonged adjunctive anticoagulation regimen of 3 months moderate-intensity coumarin, including intravenous heparinization until an international normalized ratio (INR) of 2.0 to 3.0, when compared with standard anticoagulation as adjunctive to fibrinolysis and aspirin. The Antithrombotics in the Prevention of Reocclusion In COronary Thrombolysis (APRICOT)-2 trial sought to assess the efficacy of this prolonged combined antithrombotic regimen in the prevention of reocclusion and recurrent ischemic events in patients with a patent infarct artery after fibrinolytic therapy for suspected acute myocardial infarction.

Methods

Study Protocol

The APRICOT-2 trial was an investigator-initiated, open-label, randomized angiographic and clinical follow-up study performed in 7 centers in The Netherlands between 1994 and 2000 (Figure 1). Patients with chest pain 30 minutes and ≤ 6 hours, refractory to nitrates, were treated with fibrinolytic therapy in the case of ST-elevation 0.2mV in 2 contiguous precordial leads, or 0.1mV in 2 limb leads. The agents used were anistreplase (30 U in 5 minutes), streptokinase (1.5 million units in 30 to 60 minutes), reteplase (2 bolus doses of 10 U, 30 minutes apart), or accelerated recombinant tissue-type plasminogen activator (r-tPA) (1). Patients received a starting dose of 160 mg aspirin, followed by 80 mg once daily. Adjunctive intravenous unfractionated heparin (UFH) was given for 48 hours. An intravenous bolus of 5000 U was followed by an infusion of 24000 U/24 hours, with a target activated partial thromboplastin time of twice the control. After fibrinolytic therapy, patients with clinical and/or ECG signs of reperfusion who were clinically stable were asked for informed consent. In the case of participation, coronary angiography had to be performed within 48 hours after the start of fibrinolytic therapy.

Patients were eligible to enter the study if the local investigator assessed the flow in the infarct-related artery as Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow (12). By telephone service, patients were allocated to one of two treatments by block randomization, stratified per center. In one arm the patient continued the daily use of 80 mg of aspirin, and heparin was discontinued at 48 hours. In the other arm coumarin was started in addition to 80 mg of aspirin, and heparin was continued until moderate-intensity anticoagulation was achieved, with a target INR between 2.0 and 3.0.

Follow-up angiography was scheduled at 3 months. Clinical follow-up, including bleeding complications, was collected until the second angiography. By protocol, an ischemia-guided revascularization strategy was followed (6). If angioplasty was performed before the scheduled follow-up angiography, the patency status of the infarct-related artery before dilation was considered the angiographic follow-up end point. The study was approved by the ethics review boards of the participating hospitals.

Exclusion Criteria

Patients older than 75 years, those with a contraindication to antithrombotic therapy, and those with a bypass graft as the infarct-related vessel were not eligible. Patients with a culprit stenosis that had previously been dilated, with left main stem stenosis or an unidentifiable culprit lesion patients were not included.

Coronary Angiography

The infarct-related artery was identified by correlating the coronary anatomy with the distribution of wall motion abnormality on the 30° right anterior oblique and 60° left anterior oblique ventriculograms. This information was combined with the distribution of ST-elevation on the admission ECG. If applicable, lead V_4R was used for discrimination between the circumflex artery and the right coronary artery as the infarct-related artery (6).

TIMI flow grading (12) and quantitative coronary angiographic assessment were performed at a core laboratory (Heartcore Leiden B.V., Leiden, the Netherlands), each by a different reader, blinded to the assigned strategy. The optimal single-plane projection was selected that identified the culprit stenosis in its greatest severity, with minimal foreshortening or overlapping of branches, and end-diastolic frames were chosen for quantitative angiographic analysis.

Study End Points

The primary end point was reocclusion of the infarct-related artery at angiographic follow-up, defined as TIMI grade 2 flow or less: TIMI grades 0 and 1 flow representing anatomic reocclusion and TIMI grade 2 flow functional reocclusion, as patients were included with good antegrade flow (TIMI grade 3 flow).

The secondary end point was event-free survival: a clinical course without death, reinfarction or revascularization. Mortality refers to death of all causes. Reinfarction was defined with use of the Global Utilization of Streptokinase and Tpa for Occluded coronary arteries (GUSTO)-1 trial criteria. At least 3 of the 4 criteria were required to qualify for reinfarction (13). As a safety end point, TIMI major and minor bleeding is reported (14).

Statistical Analysis

Sample Size In the APRICOT-1 trial, reocclusion occurred in 25% of patients allocated to aspirin, according to the European Cooperative Study Group criteria

(ECSG; grading 4 and 5) (7). For the present study, we anticipated a similar rate of TIMI 0-1 flow (ECSG-grade 5) as in the APRICOT-1 aspirin arm (20%). Based on differences in definition, the incidence of TIMI grade 2 flow was expected to be higher than the observed 5% of ECSG grade 4 in APRICOT-1. The estimated incidence of reocclusion for APRICOT-2 was therefore set at 30%. The trial was designed to have 80% power to demonstrate a relative reduction of 50% in the incidence of reocclusion, with a 2-sided of 5%. This would require 266 patients with angiographic follow-up. In the APRICOT-1 study, 87% of patients underwent both angiographies (7). Therefore, the target for this study was set at 305 patients. Stopping rules were not formally prespecified. Death, reinfarction, and major hemorrhage were reported to the principal investigator (FWAV) at 100 and 200 randomly assigned patients. At his discretion the trial could be prematurely discontinued.

Analysis Continuous variables were compared by the Student's t test or the Mann-Whitney U test, whenever appropriate. For comparisons between discrete variables the χ^2 test and Fisher's exact probability test were used. Analyses were performed according to the intention-to-treat principle.

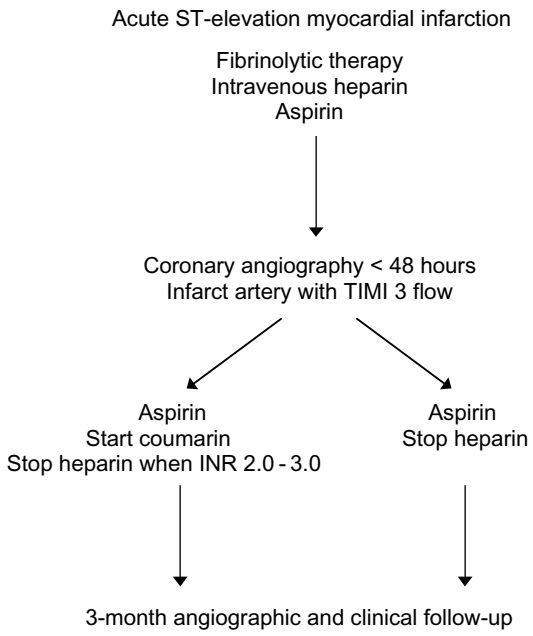

Figure 1: Design of the study

Results

In total, 308 patients were randomly assigned, of whom 34 (11%) were excluded from analysis because flow in the infarct artery was not considered TIMI grade 3 flow by the core laboratory. Follow-up angiograms of the patients with TIMI grade 2 flow at inclusion angiography were not routinely analyzed.

Clinical and angiographic baseline characteristics of the remaining 274 patients were similar to those of the 308 patients. Clinical follow-up was complete for all patients with adjudicated TIMI grade 3 flow after fibrinolysis. Fibrin-specific agents (reteplase, r-tPA) were used in 44% of patients allocated to the prolonged, combined antithrombotic regimen (59 of 135) and in 36% of those on the standard antithrombotic regimen (50 of 139; p=ns).

Angiographic follow-up was available in 251 of the 274 patients (92%). After initial consent, 19 patients (7%) refused to undergo the second angiography. Other reasons for not undergoing follow-up angiography are given in Figure 2. Baseline characteristics of patients with and without a second angiogram were not different.

Table 1 shows the baseline characteristics at the time of study entry. The treatment groups were well balanced.

Antithrombotic Medication

After the start of coumarin, heparin was continued until the target INR (2.0 to 3.0) was reached. Consequently, heparinization lasted 66 hours longer in patients allocated to the combined antithrombotic regimen, when compared with patients randomly assigned to standard heparinization and the use of aspirin alone: 110 versus 44 hours ($p < 0.01$). In 9 of 135 patients (7%) the target INR was not reached during hospitalization. Overall, heparin was discontinued in 16 patients (12%), although adequate oral anticoagulation had not (yet) been achieved. The median INR during follow-up was 2.6 (25^{th} to 75^{th} percentiles 2.1 to 3.1).

Sixteen patients (12%) randomly assigned to aspirin and coumarin did not receive the assigned antithrombotic medication (Figure 3). Three of these refused follow-up angiography, in the other 13 patients 3 reocclusions (23%) were observed. Six patients (4%) allocated to aspirin alone received additional coumarin during follow-up (Figure 3). Two of these refused angiographic follow-up, the others had TIMI grade 3 flow at the second coronary angiography. None of the patients

allocated to the standard antithrombotic regimen discontinued aspirin before follow-up angiography.

Reocclusion

Figure 4 shows the primary outcome as assessed by the core laboratory. In patients allocated to aspirin and coumarin, reocclusion was observed in 19 of 123 patients (15%), compared with 36 of 128 (28%) in patients receiving aspirin alone (relative risk [RR] 0.55; 95% CI 0.33 to 0.90, $p < 0.02$). This difference is mainly caused by a reduction in the incidence of TIMI grade 0 to 1 flow: 11 of 123 (9%) versus 25 of 128 (20%) (RR, 0.46; 95% CI 0.24 to 0.89; $p < 0.02$). Reocclusion rate for the fibrin-specific lytics was 17%, for the non-fibrin specific agents it was 24% (p = ns). No interaction between the fibrin specificity of the lytic and the allocated antithrombotic regimen was observed ($p = 0.56$).

Clinical outcome

Table 2 shows the secondary end points. Event-free survival was significantly higher in patients allocated to aspirin and coumarin compared to those in the aspirin alone arm.

Patients on the combined antithrombotic regimen had a significantly lower reinfarction rate. Of interest, in the aspirin alone group 6 of the 11 reinfarctions occurred after discharge, against 1 of the 3 reinfarctions on the combined regimen. Both in-hospital reinfarctions in the combination group occurred during continued heparinization while the target INR had not yet been reached. Of the 5 in-hospital reinfarctions in the aspirin alone group, 4 occurred within 24 hours of discontinuation of intravenous heparin.

The lower number of patients with a revascularization in the combination group was primarily caused before discharge: 5 of 135 (4%) versus 27 of 139 (19%) ($p < 0.01$). One patient in the aspirin alone arm underwent CABG after an unsuccessful urgent angioplasty. Procedure-related infarctions were seen in 3 patients allocated to the standard antithrombotic regimen and in none of those allocated to the combined regimen. From the time of random assignment, patients allocated to aspirin alone were discharged after 8 days, those receiving the combined regimen after 9 days (p = ns).

Bleeding

Bleeding complications according to the TIMI criteria occurred in 7 patients (5%) in the combination treatment group (2 major, 5 minor) and 4 (3%) in the aspirin alone group (2 major, 2 minor; p = ns). No cerebral bleeding was reported in either group. In each group 1 patient (1%) underwent blood transfusion.

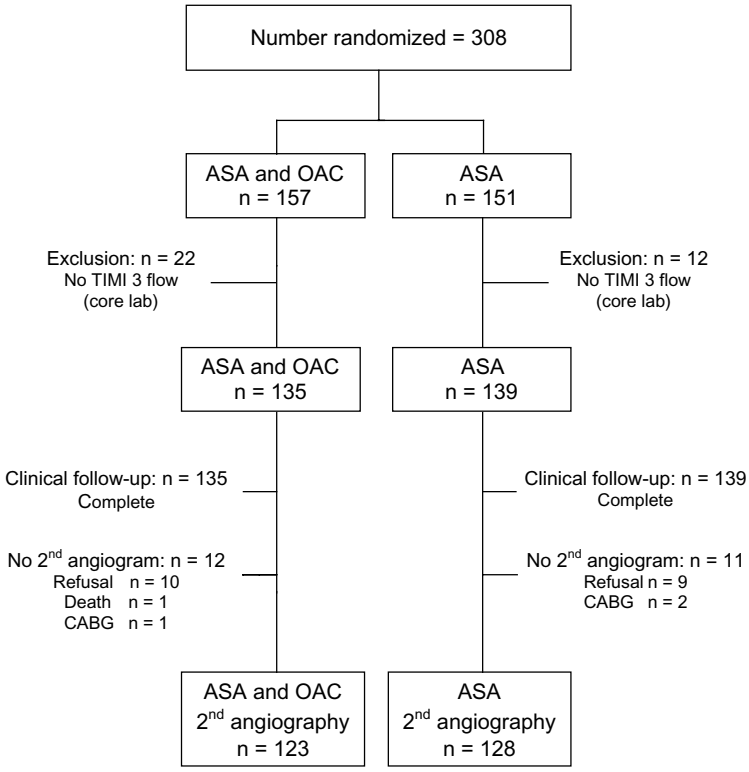

Figure 2: Flow chart showing the number of patients excluded, and the number remaining per treatment group with clinical and angiographic follow-up
ASA = aspirin; OAC = oral anticoagulation; CABG = coronary artery bypass grafting

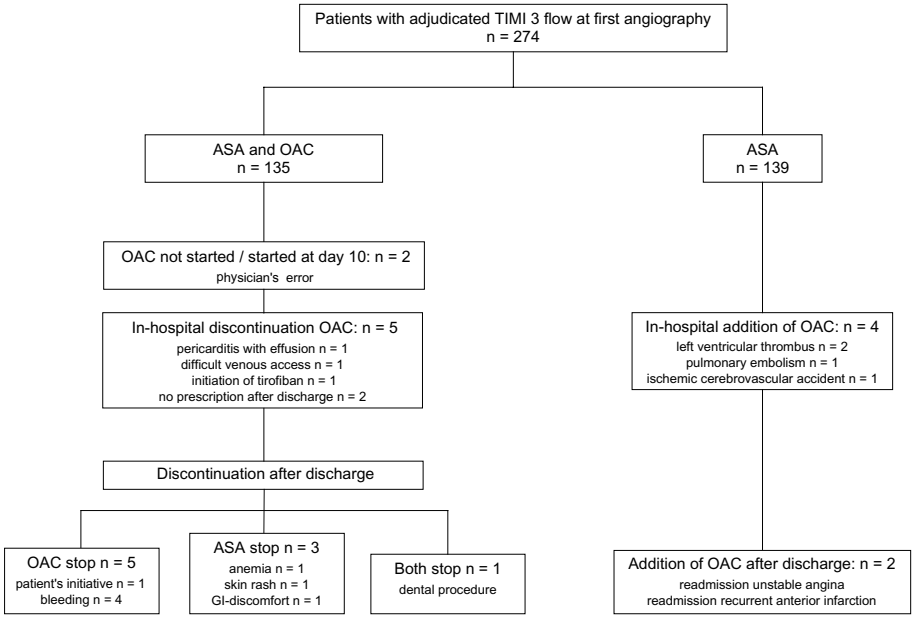

Figure 3: Changes in the assigned antithrombotic medication after random assignment
ASA = aspirin; OAC = oral anticoagulation; GI = gastro-intestinal

Table 1 Clinical and angiographic characteristics at study entry

	Aspirin and Coumadin n = 135	**Aspirin n = 139**
Men	111 (82%)	112 (81%)
Age (years)	57 ± 11	58 ± 10
Previous MI	15 (11%)	17 (12%)
Current smoker	82 (61%)	77 (55%)
Diabetes	8 (6%)	9 (6%)
Hypertension	31 (23%)	43 (31%)
Cholesterol ≥ 5.0 mmol/l	79 (59%)	86 (62%)
Time to thrombolysis (hours)	2.3 ± 1.3	2.4 ± 1.4
Median peak CK (IQR)	1034 (388-2202)	861 (496-1825)
Thrombolysis to first angio (hours)	30 ± 14	31 ± 15
Infarct-related artery:		
LAD	59 (44%)	52 (38%)
LCX	14 (10%)	27 (19%)
RCA	62 (46%)	60 (43%)
Single vessel disease	75 (56%)	75 (54%)
Culprit stenosis severity, QCA (%)	57 ± 15	59 ± 13

Data are presented as the number (%) of subjects for discrete variables, and as mean ± SD for continuous variables, except for the peak CK value.
MI = myocardial infarction; IQR = interquartile range; CK = creatine kinase; LAD = left anterior descending artery; LCX = left circumflex coronary artery; RCA = right coronary artery; QCA = quantitative coronary angiography

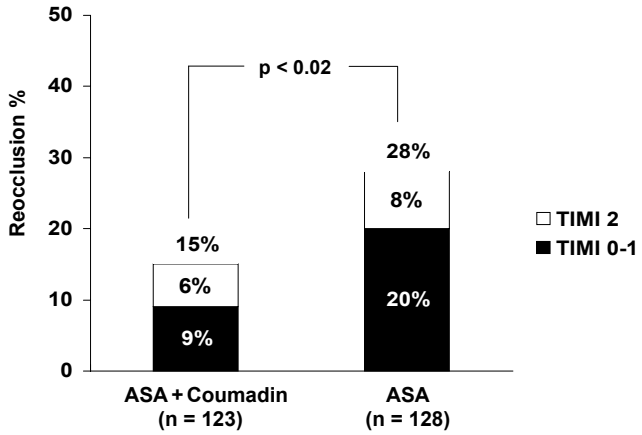

Figure 4: The incidence of reocclusion at follow-up angiography

Table 2 Clinical outcome until 3-month follow-up angiography

		Aspirin and Coumarin n = 135	Aspirin n = 139
Death		1	0
Reinfarction		3 (2%)	11 (8%) †
In-hospital		2	5
After discharge		1	6
Revascularization		17 (13%)	43 (31%) ‡
In-hospital	PTCA	5	25
	CABG	0	3
After discharge	PTCA	11	14
	CABG	1	2
Eventfree survival		116 (86%)	92 (66%) *

Data are presented as number of subjects and the proportion (%) per treatment group
Patients may have had events in more than one category
Reinfarctions presented are not procedure related (see text)
PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass grafting
* $p < 0.01$; † $p < 0.05$; ‡ $p < 0.01$

Discussion

APRICOT-2 is the largest randomized study to date with both clinical and angiographic follow-up addressing the efficacy of a continuous, combined antithrombotic regimen up to 3 months after ST-elevation myocardial infarction. The current findings in patients with an open infarct-related artery after fibrinolytic therapy are in concordance with a smaller angiographic study in a more heterogeneous population (10). In the present study, an antithrombotic regimen of aspirin, prolonged heparinization and 3 months of moderate-intensity coumarin conferred a 45% relative reduction in reocclusion as compared to standard heparinization and the use of aspirin alone.

Heparin and aspirin in acute myocardial infarction

The introduction of aspirin has markedly improved clinical and angiographic outcome after fibrinolytic therapy (5,15). With it, the routine use of subcutaneous UFH only conferred a modest additional clinical benefit, which was lost early after discharge (16,17). The limited data regarding adjunctive intravenous UFH do not suggest an important clinical benefit (17,18), despite a suggested beneficial effect on patency and reocclusion in different settings.

With conventional administration of 3 to 6 hours of r-tPA, adjunctive intravenous UFH did not result in higher 90-minute patency (19), yet an effect on 7- to 120-hour patency has been demonstrated (20,21). With regard to streptokinase, the GUSTO-1 angiographic trial did not demonstrate an effect of intravenous UFH on 90-minute patency; the impact on 24-hour patency remains unknown in lack of a placebo-controlled comparison. The best 5- to 7-day angiographic outcome after streptokinase was observed with adjunctive intravenous UFH, with comparable patency and reocclusion rates to r-tPA and intravenous UFH (1).

In view of the above, the APRICOT-2 protocol mandated that all patients received adjunctive intravenous UFH, irrespective of the fibrinolytic agent; this was to exclude selection-bias through a potential effect on patency at the time of inclusion angiography. For patients allocated to receive coumarin, heparin was continued until the target INR (2.0 to 3.0) was reached. Consequently, patients in the coumarin arm received intravenous heparin for an additional $2^1/_2$ days when compared to patients in the aspirin alone arm. This design ensured a continuous, combined antithrombotic regimen. How much prolonged heparinization in itself

has contributed to the observed effect on reocclusion and reinfarction, is beyond the scope of this trial and can not be determined in this design.

Adjunctive intravenous UFH carries the potential risk of a rebound after its discontinuation, which continuous, prolonged anticoagulation with coumarin might prevent. Interestingly, the majority of in-hospital reinfarctions in the aspirin alone group were seen within 24 hours after discontinuation of intravenous heparin, suggesting a rebound phenomenon, as observed in the GUSTO-1 trial (22). In previous trials, anticoagulation until discharge with either subcutaneous UFH (16) or the low-molecular-weight-heparin (LMWH) dalteparin (23) showed a promising in-hospital clinical benefit, which dissipated within 1 month after discontinuation. These observations, and the fact that in the present study at least half of the observed difference in reinfarction was realized after discharge support a beneficial effect of prolonged anticoagulation with coumarin (Table 2). As stated before, reocclusion is a time-dependent phenomenon with TIMI flow grade 0 to 1 rates of ~ 10% at discharge (4) and 20% at 3 months in patients using aspirin (6). Even after demonstrated patency at 4 weeks, reocclusion occurs in ~ 25% of patients within 1 year (7). Although longer heparinization may account for part of the early benefit, the continued use of oral anticoagulation after discharge seems pivotal to prevent a rebound in recurrent ischemic events and additional reocclusions.

Coumarin and aspirin in acute myocardial infarction

Dose-adjusted, frequently monitored, and individually tailored therapy is a prerequisite for optimal anticoagulation therapy, with both safety and efficacy depending on the intensity of treatment (9,24). Compliance is another important aspect, which has recently been shown to vary per country and hospital, markedly affecting efficacy (11). The large trials studying the addition of lower-intensity anticoagulation to aspirin like CARS (25) (fixed dose warfarin 1 or 3 mg/day, mean INR's 1.1 and 1.6) and CHAMP (26) (dose-adjusted, mean INR 1.8) reported more bleeding, but did not demonstrate a clinical benefit. However, the smaller APRICOT-2 and Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT)-2 trials (27) with mean INR's well above 2.0 showed improved clinical outcome. Moreover, compliance in the present study was high, with 88% of patients assigned to the combined antithrombotic regimen treated according to the protocol.

As far as inferences to daily clinical practice are concerned, this trial does not represent the general population with myocardial infarction: eligible when clinically stable, younger than 75 years, and TIMI grade 3 flow as inclusion criteria. A similar consideration holds true for the low bleeding rates in this study (24), in combination with the rather stringent TIMI bleeding criteria (14). However, the larger ASPECT-2 (mean INR 2.4) (27) and Warfarin-Aspirin ReInfarction Study (WARIS)-2 (mean INR 2.2) (24) trials, which refer to a broader population, also reported benefit from the addition of oral anticoagulation with acceptable safety. A second Scandinavian trial is Low Dose Anticoagulation and ASA Study (LOWASA) (aspirin versus aspirin plus oral anticoagulation, INR 1.0 to 1.5) which is still running and designed to include 5000 patients. In aggregate, these trials will provide a more reliable risk-benefit estimation, although the available evidence to date seems promising (24).

Implications

With the continuing search toward earlier reperfusion in a higher proportion of patients, prevention of subsequent reocclusion has inherently become an even more important issue (28). In view of the interindividual and intraindividual variability in anticoagulation with both heparin and coumarin, other agents might prove more efficacious, be it through a more predictable effect, more profound impact on the coagulation cascade, or simply better compliance. Two large angiographic trials, the Heparin-Aspirin Reperfusion Trial (HART)-2 (29) and Acute Myocardial Infarction –Streptokinase (AMI-SK) (24), showed promising findings using LMWHs after fibrinolysis. Of note, in the trials suggesting that LMWHs (Assessment of the Safety and Efficacy of a New Thrombolytic [ASSENT]-PLUS (23), ASSENT-3 (29a)) or direct Xa-inhibition (synthetic PENTasaccharide as an Adjunct to FibrinoLYsis in ST-elevation acute myocardial infarction [PENTALYSE] (29b)) are superior to intravenous UFH, administration of the new agents was continued for several days after discontinuation of intravenous heparin in the anchor arm. This in contrast to the Hirulog Early Reperfusion or Occlusion (HERO)-2 trial, in which bivalirudin administered for a similar duration as intravenous UFH resulted in lower reinfarction rates after streptokinase (30). Whereas coumarin requires regular monitoring, these agents do not, and oral direct thrombin inhibitors have recently seen the light. In anticipation of follow-up studies with the aforementioned agents, the implementation of long-term therapy with coumarin could be facilitated through self-assessed dose-adjusted anticoagulation (24).

Whether a routine invasive strategy in this study population could positively influence reocclusion and associated events remains to be determined. The available evidence to date does not support such an aggressive approach (31). This explains the symptom-driven, ischemia-guided revascularization strategy in this trial, irrespective of the presence of a severe stenosis at baseline angiography. Although the 3-month TIMI grade 0 to 1 flow rate of 9% on the combined antithrombotic regimen seems to compare favorably with the rates observed after primary PTCA with or without stenting (32), it should be realized that the current study group is much more selected. With the improved techniques and use of glycoprotein IIb/IIIa receptor blockers re-evaluation of the impact of a routine invasive strategy following successful thrombolysis seems warranted.

Limitations

As this trial was investigator-initiated and performed in an era of various consecutive large, sponsored reperfusion trials, inclusion took 6 years, which also accounts for the different types of lytics that have been used over the years. Although the observed clinical benefit seems promising, the present study is limited by its open design, sample-size and selected population. The trial was designed and powered as an angiographic study, with blind assessment of the primary end point. With clinical outcome as secondary end point, it should be considered a conceptual study, which provides insight into the mechanism underlying a potential clinical benefit.

Conclusions

The APRICOT-2 findings strongly suggest that a continuous, prolonged anti-thrombotic regimen of both anti-platelet and anticoagulation therapy has additional impact after fibrinolytic therapy. This was achieved with an acceptable safety in a high compliance setting. With respect to the implications for daily clinical practice, the results of larger trials on this and other combined antithrombotic regimens will have to be awaited.

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CHAPTER 8

Oral anticoagulation for acute coronary syndromes

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Table 1 Established indications for oral anticoagulant therapy and recommended therapeutic range

Indications	**Target INR**
Prophylaxis of venous thrombosis Treatment of venous thrombosis Treatment of pulmonary embolism Prevention of systemic emoblism • Atrial fibrillation • Tissue heart valves • Valvular heart disease	INR 2.0-3.0
• Acute myocardial infarction* Mechanical prosthetic valves (high risk)	INR 2.5-3.5
Bileaflet mechanical valve in aortic position	INR 2.0-3.0

* = as demonstrated in case A
Modified table, source (15)

The following two case presentations illustrate the range of considerations when formulating plans for oral anticoagulation in patients with acute coronary syndromes.

Case A
A 59-year old patient with a 5-hour-old transmural anterior myocardial infarction was treated with accelerated alteplase, adjunctive heparin, aspirin and a beta-blocker. Maximum CK-MB was over ten times the upper limit of normal. At day 4 echocardiography revealed a mass suggestive of a mural left ventricular thrombus, and important apical wall motion abnormalities. ACE-inhibition was initiated. To reduce the risk of systemic embolization, heparinization with a target APTT to 1.5-2.0 times control was started, followed by 6 months of dose-adjusted warfarin, target INR 2.5-3.5 (Table 1).

Case B
A 66-year old diabetic, using aspirin for a prior TIA, presented with chest pain at rest and dynamic ST-depression > 1mm. He recovered from the acute phase after treatment with low-molecular-weight heparin, nitroglycerin, aspirin and beta-blocker therapy. Cardiac markers remained negative. During the convalescence period no recurrent chest pain occurred, and exercise testing was negative with respect to symptoms and electrocardiographic signs of ischemia. Before discharge dose-adjusted medium intensity oral anticoagulation therapy (target INR 2-3) was started on top of aspirin (80 mg daily) as secondary prevention strategy for death, infarction and stroke (current update).

Background

Notwithstanding the improvements in the secondary prevention of acute coronary syndromes, death and (re)infarction still occur in ≈ 10 to 15% of patients in the 4 to 6 weeks after presentation, despite the use of aspirin. Interestingly, increased activity of the coagulation system has been reported up to six months after the index event (1). In addition, raised concentrations of factor VII are associated with both initial and recurrent ischemic events (2).

These observations stimulated renewed interest in the potential benefit of oral anticoagulants. The INR has replaced the nonstandardized prothrombin time and quick tests (3) and INR monitoring by patients is now a new feature in clinical practice (4,5). Several trials have evaluated a combined regimen of aspirin with dose-adjusted coumarins (6,7,8,9,10), 2 of which also addressed the direct comparison of both agents alone (9,10).

In view of these developments, the present report forms an update on the role of oral anticoagulation therapy in acute coronary syndromes with the emphasis on secondary prevention and its additional effect in combination with aspirin.

Pathophysiological Rationale

The process of coronary thrombosis can be divided into 3 major steps:

1. vascular injury with exposure of the thrombogenic subendothelial surface;
2. adhesion and aggregation of platelets; and
3. formation of a fibrin-rich clot

Exposure of subendothelial collagen not only activates platelets, but also the coagulation system (Figure 1). As a result, prothrombin is cleaved into thrombin by prothrombinase (factor Xa, Va and phosopholipids). Thrombin is a potent platelet activator, a process not inhibited by aspirin or clopidogrel. In addition, thrombin activates important cofactors (V and VIII) for coagulation and is the key factor in the process of fibrin clot formation. Not only does it cleave fibrinogen into fibrin, it also activates factor XIII, which results in improved clot strength with more resistance to endogenous and exogenous fibrinolysis.

In view of the above, an antithrombotic regimen of both anti-platelet and antithrombin therapy could potentially have an additional impact when compared to a regimen of anti-platelet therapy alone (Figure 1). This favors the combination of aspirin with either unfractionated heparin, low-molecular-weight heparin or a direct antithrombin in the initial hospital treatment phase in patients with acute coronary syndromes (11,12,13). After hospital discharge, recurrent ischemic events are not infrequent, and in light of the demonstrated persistent increased coagulant activity, prolonged oral anticoagulation after hospitalization might be beneficial.

Pharmacology

Oral anticoagulants such as warfarin act through interference with the vitamin K-dependent production of coagulation factors II, VII, IX, and X, which are produced by the liver (Figure 2). In addition, protein C and S, regulatory anticoagulants, are also produced in a biologically less active form after warfarin treatment. Based on their half-lives, concentrations of protein C and factor VII are the first to drop, within 24 hours of initiation of therapy, whereas levels of factors II, IX, and X fall after ≈ 4 days. This underscores the possibility of a procoagulant effect developing in a patient early after initiation or termination of oral anticoagulant therapy. Absorption of warfarin from the gastrointestinal tract is rapid, with a high bioavailability. The drug circulates bound to plasma proteins with subsequent accumulation and metabolization in the liver. Accordingly, dietary aspects related to increased or

decreased intake of the fat-soluble vitamin K, gastrointestinal malabsorption and hepatic dysfunction are some of the factors that can interfere with the response to oral anticoagulation therapy. Various drugs can cause interactions or affect the metabolic clearance of warfarin. A common interaction is with antibiotics, some potentiating (trimethoprim, metronidazol), others inhibiting (rifampicin) anticoagulant efficacy. Important for in-hospital and outpatient care in cardiology is amiodarone, which potentiates anticoagulant activity (14,15). Nonsteroidal anti-inflammatory drugs (14,15), and high doses of aspirin (> 1g/day) plus high-intensity warfarin have been associated with an increased bleeding risk (16).

Given the extent of drug interactions and range of genetic factors impacting drug disposition, interindividual and intraindividual variability in anticoagulant efficacy and safety is not surprising. However, monitoring was standardized with the introduction of the INR and results became internationally exchangeable and comparable (3). Both efficacy and safety were found to depend on the intensity of anticoagulation (14,15,17), and the maximum time spent in the target range (15). This, in turn, relates to the frequency of monitoring (15), which emphasizes the future potential of self-monitoring (4,5). In view of these developments and the lower daily doses of aspirin presently prescribed, new studies in the primary and secondary prevention of acute coronary syndromes were initiated, not only addressing the efficacy of a combined regimen with different intensities of anticoagulation but also the direct comparison of warfarin versus aspirin alone.

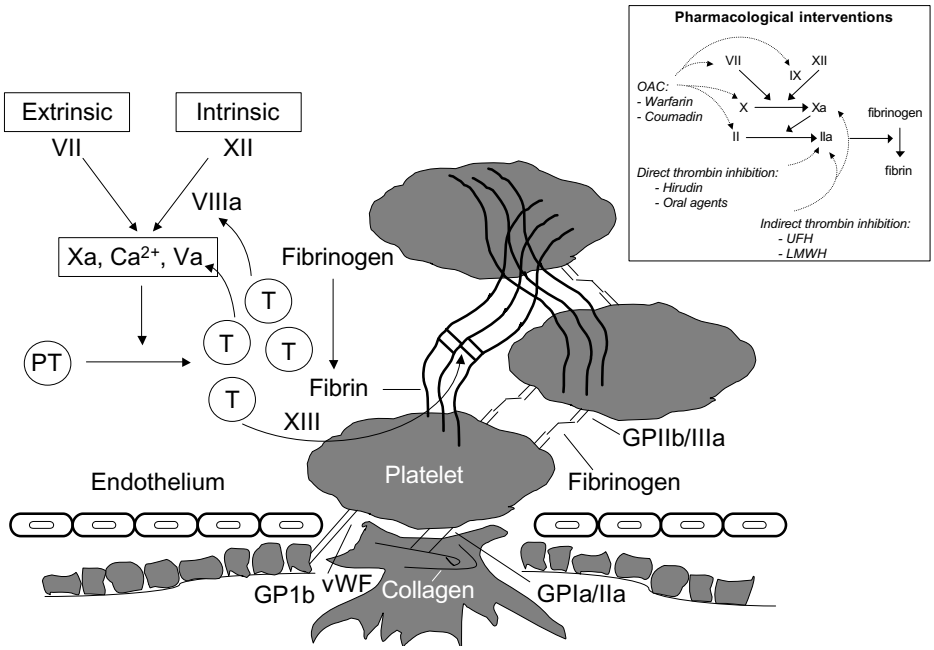

Figure 1 *Thrombus formation and pharmacological interventions in the coagulation cascade* - Tissue injury not only induces subendothelial adhesion (vWF, GP 1b, GP Ia/IIa) and aggregation of platelets (fibrinogen, GPIIb/IIIa), but also activates the coagulation cascade. Activation of the extrinsic and intrinsic coagulation pathways results in the thrombin-induced formation of a fibrin-rich clot. Fibrin cross-linking by factor XIII improves clot-strength. Whereas oral anticoagulants interfere with the production of coagulation factors, other agents inhibit the action of activated clotting factors.
vWF = von Willebrand factor; PT = prothrombin (II);T = thrombin (IIa);
OAC = oral anticoagulants; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin

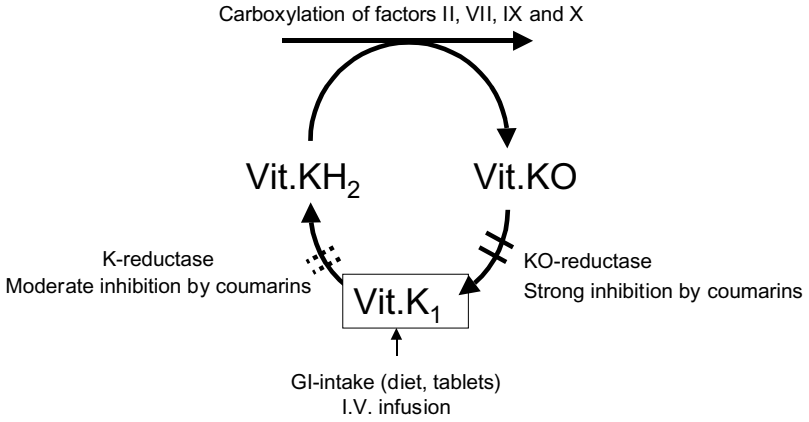

Figure 2 *Oral anticoagulants – Mechanism of action*
Coumarins inhibit the conversion of vitamin K epoxide (Vit.KO) to its reduced form (Vit. KH2) through interference with two reductases: KO-reductase and K-reductase. Subsequent insufficient gamma-carboxylation results in coagulation factors with impaired biological function. Most of the impact is exerted through inhibition of the coumarin-sensitive KO-reductase. As K-reductase is relatively coumarin resistant, dietary aspects and administration of vitamin K (Vit.K1) are interfering factors. (modified figure, source (15))

Clinical Efficacy

Primary Prevention

Dose-adjusted low intensity warfarin (target INR 1.3 to 1.8) has been shown to reduce the risk of ischemic heart disease to an extent similar to 75 mg of aspirin. Interestingly, warfarin (mean INR, 1.5) primarily reduced fatal events and aspirin nonfatal myocardial infarction. The combination of warfarin and aspirin had additional beneficial impact, but increased fatal strokes and minor bleeding. The use of either agent alone was associated only with more minor bleeding (18). Similar to primary prevention studies with aspirin (19), the benefit of oral anticoagulant therapy in primary prevention is confined to high-risk men, with little data available for women.

Secondary Prevention

Monotherapy versus control. Oral anticoagulation is one of the oldest strategies of secondary prevention of ischemic heart disease. After a large number of controlled trials in the 1960s, 2 large double-blind placebo-controlled randomized

trials in the early 1990s unequivocally demonstrated the efficacy of full-intensity anticoagulation (INR, 2.8 to 4.2), at the cost of a 4-fold increased risk of major bleeding (17,20,21).

Monotherapy versus aspirin. Given its ease of administration and favorable safety profile, aspirin has become the initial antithrombotic agent of choice in acute coronary syndromes. Meta-analysis on the few small trials comparing moderate-to-high intensity anticoagulation versus aspirin did not demonstrate a difference in efficacy, whereas bleeding was lower on aspirin (17). Interestingly, the recently presented ASPECT-2 (target INR, 3.0 to 4.0) and WARIS-2 (target INR, 2.8 to 4.2) trials both reported that full-intensity anticoagulation as monotherapy was superior to aspirin alone in the secondary prevention of death, (re)infarction, and stroke (9,10). Thus, high-intensity oral anticoagulation seems an effective alternative for aspirin in the setting of well-organized frequent INR monitoring.

Combination therapy versus aspirin alone. Oral anticoagulation therapy at medium-high and low intensity combined with aspirin has been tested (Table 2). A combination of medium-high intensity oral anticoagulation plus aspirin seems promising (17), whereas fixed-dose, low intensity does not improve clinical outcome (22). Since the start of the new millennium, 4 trials with a target INR > 2 have been completed, 3 involving patients with myocardial infarction (8,9,10), and 1 that primarily included patients with unstable angina (6). APRICOT-2 and ASPECT-2 were performed in the Netherlands (8,9) and WARIS-2 in Norway (10), countries that are known for the high quality of their anticoagulation clinics. ASPECT-2 was unfortunately prematurely discontinued due to slow recruitment. Although underpowered, a significant clinical benefit for the combined antithrombotic regimen (reached INR, 2.4) was observed when compared to aspirin alone (9). In APRICOT-2, designed and powered as angiographic follow-up trial, the combined antithrombotic regimen (reached INR, 2.6) produced a 40% reduction in 3-month reocclusion after successful fibrinolytic therapy. Similar findings were observed in a smaller, more heterogeneous group of patients after acute coronary syndromes. Clinical outcome, the secondary end point, was also significantly improved (8,23). The large WARIS-2 trial (INR, 2.2) confirmed these observations over a 4-year follow-up period, with a reduction in the combined end point of death, reinfarction and stroke from 20% to 15% (10). OASIS-2 was performed worldwide, and showed a non-significant 10% reduction for the combined strategy (6). When OASIS-2 was reanalyzed, stratified by countries with good compliance to anticoagulation

therapy a marked clinical benefit was apparent (Table 2). The largest worldwide trial after myocardial infarction to date, CHAMP, was aimed at a target INR of 1.5 to 2.5, and was neutral. In this trial, with a mean INR of 1.8, most patients had an INR near the lowest target intensity (7).

In aggregate, the available data suggest that in a setting of good compliance and well-organized INR monitoring, addition of oral anticoagulation (INR, > 2.0) to aspirin seems beneficial. More insight into the efficacy and safety of a regimen with a target of 1.5 to 2.5 will be provided by the LOWASA study, which is enrolling > 5000 patients in Sweden.

Clinically observed mechanism of benefit

The controlled trials of warfarin as a single agent showed marked reductions in death, (re)infarction and stroke, respectively (17). As for the direct comparison with aspirin, or a specification of the efficacy of the combined regimen, an updated meta-analysis including final data of the unpublished trials is warranted. The fact that oral anticoagulants take 2 to 4 days to become therapeutically effective is an important clinical consideration. Timing of initiation of oral anticoagulation and the antithrombotic regimen administered during the acute phase therefore must take into account such pharmacological factors.

Adverse Events

In patients taking oral anticoagulants, the initiation or withdrawal of concurrent medications must be reviewed by a health care professional, preferably a member of a dedicated anticoagulation service committed to close communication with the patient. The most frequent complication is bleeding, which is related to the intensity of anticoagulation (14,15,17) and is more frequent when oral anticoagulation is used in patients with cerebrovascular or peripheral disease (24). High-risk subgroups are those with a history of gastro-intestinal bleeding, stroke, hypertension, impaired renal function and anemia. Whether increased age is an independent risk factor, or whether bleeding is primarily a result of comorbid factors remains an issue of controversy. Irrespective of age, bleeding episodes should trigger a search for a possible underlying occult lesion, which may be malignant (14,15). With respect to the safety of a combined regimen of aspirin and dose-adjusted oral anticoagulation therapy, the different studies report a 2- to 3-fold increased risk of minor and major bleeding, without an increased risk of intracerebral hemorrhage (6,7,8,9,10).

A less frequently observed side effect is skin necrosis attributable to thrombosis of the venules and capillaries within the subcutaneous fat. An abrupt drop in protein C levels or a preexisting deficiency is held responsible for the procoagulant response seen in the first 3 to 8 days after initiation of therapy (14,15).

It should be noted that oral anticoagulants are associated with an increased risk of fetal central nervous system and bone abnormalities, bleeding and fetal death. For most pregnant women requiring anticoagulant therapy, unfractionated heparin and subcutaneous low-molecular-weight heparin are safe alternatives (14,15).

Table 2

Study	Year	N	INR target	INR reached	ASA dose (mg)	1° Endpoint ASA+OAC	1° Endpoint ASA	RR	p Value	Fup (months)
Angiographic						*% (re)occlusion*				
Williams [23]	1997	57	2.0-2.5	2.0	150	4%	33%	n.a.	0.02*	3
APRICOT-2 [8]	2000	310	2.0-3.0	2.6	80	18%	30%	0.60 (0.39-0.93)	0.02	3
Clinical						*% mortality,(re)MI,stroke*				
CARS [22]	1997	8,803	1 mg qd		80 vs. 160	8.8%	8.6%	1.03 (0.87-1.22)	0.74	14
			3 mg qd			8.4%		0.95 (0.81-1.12)	0.57	14
CHAMP [7]	1999	5,059	1.5-2.5	1.9	80 vs. 160	17.6%†	17.3%†	0.98 (0.87-1.11)	0.76	33
ASPECT-2 [9]	2000	668	2.0-2.5	2.4	80	5.1%	9.2%	0.55 (0.31-0.98)	< 0.05	12
OASIS-2 [12]	2001	3,712	2.0-2.5	n.p.	Not specified	7.6%	8.3%	0.90 (0.72-1.14)	0.40	5
Good compliers		1,821				6.1%	8.9%	0.68 (0.48-0.95)	0.02	
Poor compliers		1,891				9.0%	7.8%	1.17 (0.86-1.60)	0.33	
WARIS-2 [10]	2001	2,414	2.0-2.5	2.2	75 vs. 160	15.0%	20.0%	0.71 (0.58-0.86)	< 0.01	48

Unpublished data are shown as presented at the respective congresses, and are preliminary results.
* = p-value by Fisher exact test
† = mortality, primary endpoint
N = number of patients randomized
INR = international normalized ratio
ASA = aspirin
OAC = oral anticoagulation
1° Endpoint = primary endpoint
RR = relative risk
Fup = follow-up period
Good/poor compliers: oral anticoagulation use in over/less than 70% patients at 35 days
n.a. = not applicable
n.p. = not published

Recommendations

Irrespective of the indication, dose-adjusted, frequently monitored and individually tailored therapy is a prerequisite for optimal oral anticoagulation. Primary prevention can be considered in high-risk patients with difficult or nonmodifiable risk factors, aiming at a target INR of 1.5 (18). In patients with an acute coronary syndrome oral anticoagulation should be prescribed for established indications (eg, case A, (15), Table 1) in the absence of contraindications. Secondary prevention of coronary events attributable to recurrent thrombosis is a major component of management of patients after presentation with an acute coronary syndrome. Given its ease of administration, predictable safety, and proven efficacy, aspirin should be the preferred agent for this indication (19).

In clinical settings with a good infrastructure, full-intensity oral anticoagulation (target INR, 2.8 to 4.2) is an effective alternative, with ample evidence-based support (9,10,17). If aspirin is contraindicated, oral anticoagulation is the only effective alternative long-term antithrombotic regimen so far tested in patients after ST-elevation myocardial infarction. Although both low-molecular-weight heparin and clopidogrel in addition to aspirin have been proven safe in the long-term treatment after a non ST-elevation acute coronary syndrome (25,26), only clopidogrel proved to be of additional benefit. In cases of aspirin intolerance, 75 mg of clopidogrel once daily seems a practical long-term alternative. With respect to the long-term benefits of clopidogrel (27), direct comparisons with oral anticoagulation, both as single agents and in addition to aspirin, have not been performed to date. We believe this is an important area for future trials.

Data on the combination of moderate intensity anticoagulation (target INR, 2 to 3) with aspirin seem promising (6,8-10,17), but routine implementation can not (yet) be recommended in uncomplicated patients (eg, Case B). Combination therapy can certainly be considered in individual (high-risk) cases; in that case, the recommended aspirin dose is 80 mg daily (7-10,22) to be taken along with moderate-intensity oral anticoagulation. Definition of the optimal duration of therapy and identification of subsets of patients with the optimal risk-benefit profile are relevant clinical issues. A practical aspect of concern is the fact that even in countries with an established good quality anticoagulation service infrastructure and high short-term compliance, ≈ 20 to 25% of patients discontinue therapy within 6 months, and only a minority do so as a result of bleeding (6,9).

Conceptually, the observed benefits of anticoagulant therapy in addition to an antiplatelet regimen call for the search of a less cumbersome long-term alternative, that is at least as effective as warfarin, but with less intraindividual and interindividual variability. For patients after ST-elevation myocardial infarction, data on low-molecular-weight heparin seem promising in hospital (28) and consideration should be given to trials of long-term therapy in that patient subset. For the entire spectrum of patients recovering from an acute coronary syndrome, agents without the need for hematologic monitoring, such as Xa inhibitors (29,30) and oral direct thrombin inhibitors, seem appealing candidates for additional study.

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CHAPTER 9

High-grade infarct related stenosis after successful thrombolysis: strong predictor of reocclusion, but not of clinical reinfarction

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Abstract

Background: After successful thrombolysis a high-grade stenosis at 24-hour angiography strongly predicts reocclusion, and is often believed to result in high reinfarction rates. However, routine angioplasty did not reduce death or reinfarction in past trials. Importantly, systematic angiographic follow-up shows that reocclusion often occurs without clinical reinfarction. This study investigates whether the increased risk for reocclusion associated with a high-grade lesion translates into impaired clinical outcome.

Methods: In the ischemia-guided APRICOT-1 trial 240 ST-elevation MI patients with an open infarct artery 24 hours after thrombolysis had 3-month repeat angiography to assess reocclusion with clinical follow-up at 3 months and 3 years.

Results: Based on the optimal discriminative stenosis severity, reocclusion was 40% (47/118) in patients with a high-grade residual stenosis and 16% (20/122) in those with a low-medium-grade lesion (RR 2.43, 95% CI 1.54-3.84, p<0.01). Three-month death and reinfarction did not differ: 6% (7/118) versus 9% (11/122) (RR 0.66, 95% CI 0.26-1.64, p=ns). Systematic angiographic follow-up revealed that reocclusion of a high-grade lesion occurred in the absence of clinical reinfarction in 85% (40/47) as compared to 45% (9/20) in patients with a low-medium-grade stenosis (RR 1.89, 95% CI 1.15-3.12, p<0.01). Despite an independent association with reocclusion, a high-grade stenosis predicted neither short- nor long-term death and reinfarction.

Conclusions: Following an ischemia-guided strategy after successful thrombolysis, patients with a high-grade stenosis experience similar death/reinfarction rates as patients with a low-medium-grade lesion. This, despite a two- to threefold higher risk for reocclusion. The finding that reocclusion of a high-grade lesion often occurs without clinical reinfarction, explains the absence of a relationship between a severe stenosis and death/reinfarction. Appreciation of these observations may contribute to an optimal design of a future randomized trial to re-evaluate the impact of a routine invasive strategy.

Introduction

Despite the undisputed benefits on early infarct artery patency and clinical outcome (1), the initial success of thrombolytic therapy is often partly offset by reocclusion. Reocclusion occurs in ~30% of patients within the first year after acute myocardial infarction (2-4) and portends adverse short- and long-term outcome (5-7).

Past observations suggested a relationship between a high-grade residual stenosis and reocclusion after successful thrombolysis (8-11). It was assumed that reocclusion of a high-grade stenosis leads to a high incidence of death, reinfarction and recurrent ischemia (8-12). Unexpectedly, a meta-analysis on routine angioplasty did not show reduced death and reinfarction rates as compared to an ischemia-guided revascularization strategy, which was attributed to high peri-procedural event rates (13). Unfortunately, angiographic reocclusion was not addressed in those trials. Later studies demonstrated that reocclusion occurs asymptomatically in up to two-thirds of patients, that is without death or clinical reinfarction (3,5,6); collateral supply to the infarct area has been suggested as a potential mechanism (14).

Given the absence of a 1:1 relationship between reocclusion and these events, the attainable benefit from angioplasty to reduce death or reinfarction depends on the proportion of symptomatic reocclusions occurring in patients with a severe stenosis.

The Antithrombotics in the Prevention of Reocclusion In COronary Thrombolysis (APRICOT)-1 trial (2) was performed in the same era as the trials in the meta-analysis. In this angiographic and clinical follow-up trial an ischemia-guided revascularization strategy was followed, irrespective of the presence of a high-grade stenosis. In this setting, we previously demonstrated that stenosis severity 24 hours after successful thrombolysis was the only independent predictor of reocclusion (15).

In the current analysis we dichotomized our study population according to the optimal quantitative stenosis severity cut-point to predict reocclusion. Subsequently, we sought to assess whether the increased risk for reocclusion in patients with a high-grade stenosis at 24-hour angiography translates in impaired clinical outcome in both the short- and the long-term.

Methods

Protocol

The APRICOT-1 study protocol has been reported in detail previously (2). In brief, 300 patients < 71 years old with chest pain lasting > 30 minutes and < 4 hours, and 0.2 mV ST-segment elevation in at least 2 contiguous leads on the electrocardiogram (ECG), received thrombolysis for suspected myocardial infarction followed by 20,000 U of intravenous heparin/24h. In the case of clinical and/or electrocardiographic signs of reperfusion, clinically stable patients were asked informed consent to undergo coronary angiography within 48 hours after thrombolysis. The infarct-related artery was identified using previously described methods (2) and in the case of a patent artery, grade 1 to 3 stenosis according to the European Cooperative Study Group (ECSG) criteria (Table I), patients were eligible for the study. Sixteen patients were retrospectively excluded for not having a patent infarct artery at baseline angiography according to the blinded angiography committee.

The 284 patients with a patent infarct artery were randomly allocated to one of three arms: blinded treatment with either 325 mg of aspirin or placebo, or open-label coumadin including continued heparinization until the target INR (2.8-4.0) was reached. By protocol revascularization was only to be performed for recurrent ischemia refractory to maximal anti-ischemic medication. To assess reocclusion follow-up angiography was scheduled at three months. If coronary angioplasty (PTCA) was performed before the planned repeat angiography, the patency status of the infarct artery before dilatation was scored as follow-up endpoint.

At baseline angiography quantitative coronary angiography (QCA) of the culprit lesion was performed, providing a precise estimation of the diameter stenosis with low intra- and interobserver variability (16). For this analysis the optimal single projection with the most severe measured stenosis was used. Morphology of the culprit lesion was scored according to Ambrose et al. (17). Collateral filling of the infarct artery was assessed at both angiograms according to the Rentrop grading system (18).

Three-month clinical follow-up data included survival, reinfarctions, revascularizations and recurrent ischemia. Follow-up on survival and reinfarction was extended over a 3-year period. Information was derived from medical charts, municipal registries, or by telephone contact with the patient, relatives or the general practitioner.

Definition of patient groups and endpoints

Based on the optimal stenosis severity cut-point to predict reocclusion the study population was dichotomized in patients with a high-grade or a low-medium-grade stenosis. Patients were followed for death and reinfarction until the day of 3-month repeat angiography. A patient with a reoccluded infarct artery at urgent repeat angiography performed for clinical reinfarction was considered to have a so called "symptomatic" reocclusion.

The definition of reocclusion was ECSG grade 4 or 5 (2). Clinical reinfarction was defined as recurrent ischemic symptoms lasting > 30 minutes accompanied by transmural ischemia in the same ECG area as the index infarction with elevated creatine kinase levels. At follow-up visits a careful patient history was taken and the ECG was screened for new Q-waves in order to detect possible silent reinfarctions.

In addition to death and reinfarction, revascularizations were scored as well as the incidence of recurrent ischemia until the day of follow-up angiography. Recurrent ischemia was defined as recurrent chest pain during stress testing or at rest, accompanied by electrocardiographic signs of ischemia.

To study the prognostic impact of stenosis severity in the long-term, infarct-free survival at 3-year follow-up was assessed.

Statistics

Statistical analysis was performed with SPSS 9.0 (SPSS Inc. 1999, Chicago, USA). Receiver operating characteristics (ROC) analysis was performed on QCA stenosis as a predictor of reocclusion. The optimal cut-point level for stenosis severity was obtained with Fisher's linear discriminant analysis.

To test differences between groups the Student's t test, Mann-Whitney-U-test or χ^2-test were used whenever appropriate. Statistical significance was defined as a two-sided p-value < 0.05.

Multivariable logistic regression analysis was used to determine the association between a high-grade stenosis and 1) reocclusion; 2) short-term death and reinfarction. Variables included in the multivariable model were those causing imbalances in baseline characteristics (see results) combined with 1) univariate predictors of reocclusion (15) and 2) TIMI-risk score variables associated with clinical outcome (19). Long-term event-free survival analysis was performed according to Kaplan and Meier, using the log-rank test for comparison between

groups. Cox-regression analysis was used to assess a possible independent relationship between stenosis severity and long-term infarct-free survival.

Table 1 European Cooperative Study Group classification

Stenosis grade	
0	Normal
1	< 50% diameter stenosis
2	50% to 90% diameter stenosis
3	91% to 99% diameter stenosis, complete filling within 3 cycles
4	91% to 99% diameter stenosis, no complete filling within 3 cycles
5	Total occlusion with or without collateral filling

Results

Out of the 284 patients participating in the APRICOT-1 trial the current study group consists of the 240 patients with two angiograms and complete QCA-analysis. Thirty-six patients did not undergo follow-up angiography for reasons of refusal (n=28), coronary bypass surgery (n=6) or death (n=2). In 8 patients QCA-analysis was technically not possible. These 44 patients did not differ from the study group except for a tendency towards older age (59 $\pm$ 9 versus 56 $\pm$ 9 years, p=0.06).
Figure 1 shows the distribution of the quantitatively assessed severity of infarct related stenoses. Baseline angiography was performed at a mean of 24 $\pm$ 14 hours. Stenosis severity was not related to the timing of the first angiogram. Follow-up angiography was performed after a mean of 75 $\pm$ 31 days.

Optimal diameter stenosis cut-point level for reocclusion

ROC analysis to determine the optimal QCA stenosis severity to predict reocclusion is shown in Figure 2. Diagnostic accuracy of QCA stenosis to predict reocclusion was moderate. Fisher's linear discriminant analysis identified a 62.7% residual diameter stenosis at baseline as the optimal cut-point level for reocclusion. Sensitivity was 70%, with a negative predictive value of 84%.
This cut-point level dichotomized the study population in two groups:

- a group of 118 patients with a high-grade stenosis (QCA $\geq$ 62.7%) at high risk for reocclusion (40%; 47/118), and
- a group of 122 patients with a low-medium-grade stenosis (QCA < 62.7%) at lower risk for reocclusion (16%; 20/122)

This difference (40% vs. 16%) represents an unadjusted relative risk for reocclusion of 2.43 (95% CI 1.54-3.84, p<0.01) for patients with a high-grade stenosis at baseline.
Baseline characteristics are shown in Table 2. Smoking (70%), hypercholesterolemia (57%), diabetes (6%) and hypertension (26%) did not differ between groups. In patients with a high-grade stenosis a higher occurrence of smooth culprit lesions and a tendency towards more previous angina were observed.

High-grade stenosis and death/reinfarction

Figure 3 shows the incidence of reocclusion and the incidence of death or reinfarction. Interestingly, despite the two- to threefold increased risk for reocclusion

in patients with a high-grade stenosis, the incidence of death or reinfarction did not differ from patients with a low-medium-grade lesion: 6% (7/118) and 9% (11/122), respectively (RR 0.66, 95% CI 0.26-1.64, p=ns).
Systematic angiographic follow-up revealed that overall 73% (49/67) of reocclusions occurred in the absence of clinical reinfarction. Proportionally, reocclusion occurred more often without clinical reinfarction in patients with a high-grade stenosis than in patients with a low-medium-grade lesion: 85% (40/47) versus 45% (9/20), respectively (RR 1.89, 95% CI 1.15-3.12, p<0.01).

Recurrent ischemia and revascularization

Recurrent ischemia was seen in 32% (38/118) of patients with a high-grade stenosis and 27% (33/122) of patients with a low-medium-grade lesion (RR 1.19, 95% CI 0.80-1.76, p=ns). In aggregate, revascularization rate was 11% (26/240): 14% (16/118) in patients with a high-grade stenosis and 8% (10/122) in patients with a low-medium-grade lesion (RR 1.65, 95% CI 0.78-3.50, p=ns).
Of all patients who were conservatively managed for recurrent ischemia, only one patient suffered a reinfarction, that occurred after hospital discharge. This patient had a < 50% stenosis at 24-hour angiography.

Collaterals

Out of the 67 patients with reocclusion, the presence and quality of the collateral filling of the infarct artery could be assessed in 63 (94%). At baseline angiography none of these patients had good collaterals.
At follow-up angiography good collaterals were seen in 61% (27/44) of patients with a high-grade baseline stenosis and 42% (8/19) of patients with a low-medium-grade baseline lesion: RR 1.46, 95% CI 0.82-2.60, p=0.15.

Multivariable analysis

Multivariable analysis identified a high-grade QCA-stenosis as an independent predictor of reocclusion: OR 3.36, 95% CI 1.81-6.26, p<0.01. During the time period from baseline angiography until the day of repeat catheterization a high-grade stenosis was not a predictor of death or reinfarction: OR 0.61, 95% CI 0.22-1.67, p=ns. Morphology of the culprit lesion predicted neither reocclusion, nor clinical outcome.

Long-term follow-up

Median long-term clinical follow-up from the time of randomization was 858 days (25^{th}-75^{th} percentiles: 565-1293). At 3-year follow-up survival free from reinfarction was 81% in patients with a high-grade stenosis as compared to 82% in patients with a low-medium-grade stenosis (Figure 4, p=ns). A high-grade stenosis at baseline was not a predictor of long-term death and reinfarction: HR 0.99 , 95% CI 0.53-1.85 (Cox-regression, p=ns).

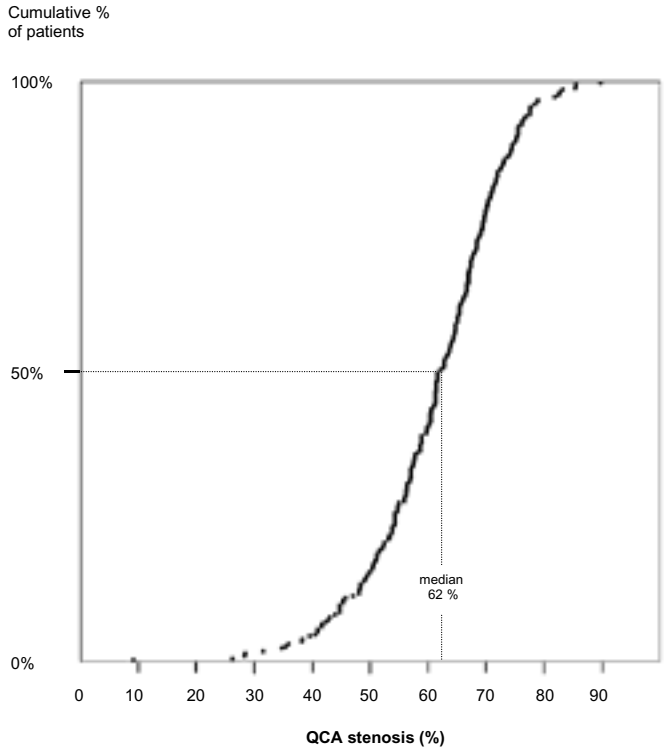

Figure 1: Distribution of the quantitatively assessed severity of the infarct related stenoses at 24-hour angiography

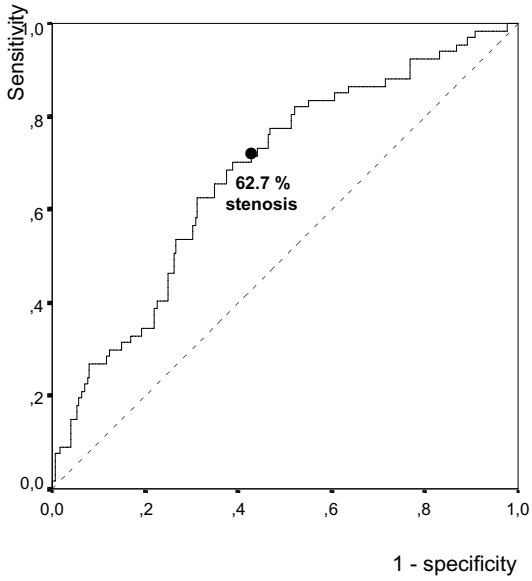

Figure 2: ROC analysis for QCA stenosis as predictor of reocclusion (area under the curve 0.680, 95% CI 0.605-0.754, $p < 0.01$)

Table 2 Baseline characteristics

	High-grade stenosis n = 118	**Low-medium-grade stenosis n = 122**
Men (%)	99 (84%)	100 (82%)
Age (years)	56 ± 9	56 ± 9
Previous angina		
< 4 weeks	41 (35%)	31 (25%)†
≥ 4 weeks	25 (21%)	23 (19%)
Previous myocardial infarction	7 (6%)	8 (7%)
Time symptoms – thrombolysis (hr)	2.1 ± 1.0	2.0 ± 1.0
Thrombolytic		
Streptokinase	101 (86%)	109 (89%)
Anistreplase	117 (14%)	113 (11%)
Peak creatine kinase (units/L)*	1086	1100
(IQR)	(454-1941)	(624-2211)
Time thrombolysis – first angiography (hr)*	22	22
(IQR)	(13-31)	(14-33)
Anterior infarction	44 (37%)	55 (45%)
Single vessel disease	62 (53%)	73 (60%)
% stenosis QCA	70.5 ± 5.5	52.3 ± 9.1‡
Lesion type		
Smooth	74 (63%)	61 (50%)§
Complex	44 (37%)	61 (50%)
Antithrombotic regimen		
Coumadin	37 (31%)	42 (34%)
Aspirin	49 (42%)	41 (34%)
Placebo	32 (27%)	39 (32%)

Data are presented as the number (%) of subjects for discrete variables, and as mean ± standard deviation for continuous variables unless indicated otherwise.

* median; IQR = Interquartile range; † $p = 0.07$ for previous angina versus no previous angina, ‡ $p < 0.01$, § $p < 0.05$

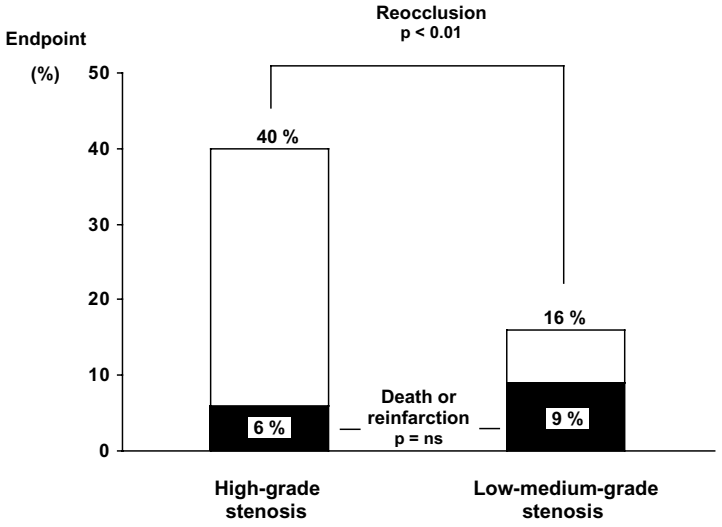

Figure 3: Incidence of reocclusion in patients with a high-grade stenosis (n=118) and a low-medium-grade stenosis (n=122)
Death and reinfarction rates dashed.

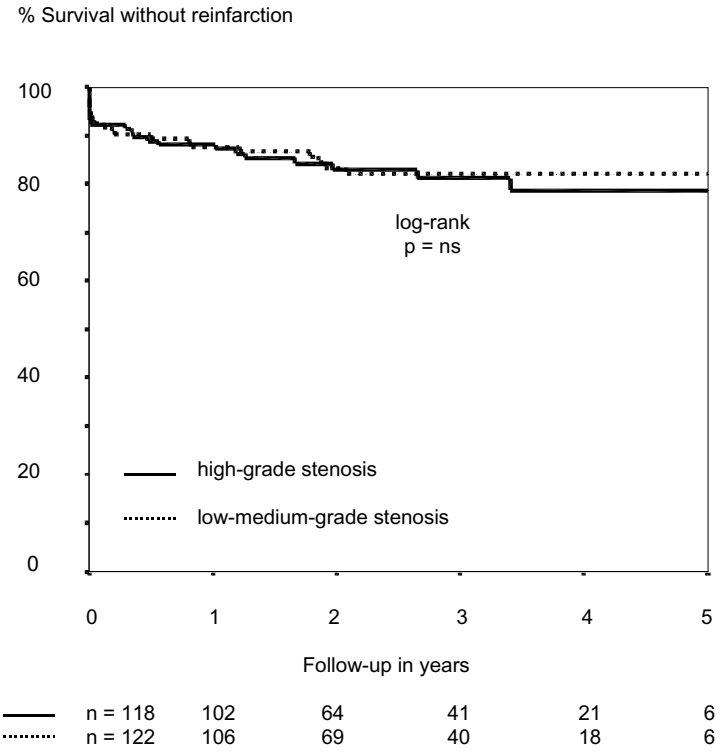

Figure 4: Event-free survival, defined as a clinical course without death or reinfarction

Discussion

This analysis on 240 patients with successful thrombolysis, in whom an ischemia-guided revascularization strategy was followed, is the largest observation to date on the relationship between residual stenosis severity, reocclusion, death and reinfarction. In contrast to what is generally believed, patients with a high-grade residual stenosis – optimized to predict reocclusion – did not experience adverse clinical outcome when compared to patients with a low-medium-grade lesion; this, despite a two- to threefold higher risk of reocclusion. Although the absence of an association between stenosis severity and clinical outcome has been reported before (20), the current data provide insight into a potential underlying mechanism. Moreover, an additional explanation is postulated for the lack of benefit observed in past trials on routine angioplasty after successful thrombolysis.

Rationale of past angioplasty trials

The current observations are in contrast to the hypothesis that formed the basis of previous trials studying routine angioplasty after successful thrombolysis. These trials were based on 2 premises: 1) a suggested relationship between a high-grade residual stenosis and reocclusion, and 2) the assumption that, with this increased risk for reocclusion, the subset of patients with a high-grade lesion could be identified as a high-risk group for death and reinfarction (8-12). Consequently, reduction of the residual lumen narrowing was thought to reduce the incidence of reocclusion and subsequently to lead to improved clinical outcome (8,9). However, meta-analysis of the randomized trials did not show a benefit on death and reinfarction for routine angioplasty after successful thrombolysis when compared to an ischemia-guided strategy (13). This was attributed to high peri-procedural event rates.

The premises on which these trials were based have never been questioned, although at the time of initiation they were derived from small observational studies involving selected patients (8-12). Later reports from large angiographic trials consistently showed an association between stenosis severity and reocclusion, although an independent relationship has only been demonstrated in patients undergoing delayed angiography, having survived the first 24-48 hours or more (5,15,21-23).

Stenosis severity, reocclusion and recurrent events

It has also been demonstrated that reocclusion is associated with adverse clinical outcome (5-7,24). Given the markedly increased risk for reocclusion in patients with a high-grade stenosis, it is temptative to consider these patients at higher risk for death or reinfarction than patients with a low-medium-grade lesion. Trials on routine angioplasty after successful thrombolysis were already ongoing, when it was shown that reocclusion occurs without without death or clinical reinfarction in up to two-thirds of patients (3,5,6). Inherently, the degree of clinical benefit attainable with routine angioplasty largely depends on how often reocclusion of a high-grade stenosis occurs with these events. The unique design of the APRICOT-1 trial allowed us to study this question. Clinical and angiographic follow-up were assessed simultaneously at the day of repeat angiography and the analysis included patients undergoing early angiography for recurrent ischemia. Importantly, the rather conservative revascularization strategy in this trial (overall revascularization rate 11%) offers unique insight into the "natural clinical course" following successful thrombolysis.

It was found that, despite a two- to threefold increased risk for reocclusion, patients with a high-grade residual stenosis experienced similar short- and long-term clinical outcome when compared to patients with a low-medium grade stenosis (Figure 3,4). At first glance, this may seem unexpected: yet, while only one out of six patients with a reocclusion on a high-grade stenosis presented with clinical reinfarction, this was the case in about one out of every two patients with a reocclusion on a low-medium-grade lesion.

The clinical presentation of reocclusion may also be affected by the presence and quality of collateral supply to the reoccluded infarct artery, and factors as the viability of the myocardium distal to the culprit and the presence of diabetes (less pain perception).

Our finding that stenosis severity after successful thrombolysis is not related to short-term clinical outcome not only complements observations from a previous study with 90-minute angiography (20), but also extends into the long-term. The fact that patients with a high-grade stenosis were somewhat more likely to undergo revascularization in case of recurrent ischemia does not seem to have affected death and reinfarction rates: of all patients with recurrent ischemia who were not revascularized, only one patient (stenosis < 50% at baseline) suffered a reinfarction.

Thus, even in the setting of a rather conservative, ischemia-guided strategy a high-grade stenosis did not predict clinical reinfarction, despite the associated high-risk for reocclusion. Also with stenosis severity as continuous variable, ROC-analysis was unable to detect a predictive cut-off level for clinical reinfarction (data not shown).

Implications

Although the current observations should be considered as hypothesis generating, they may carry important considerations for a future prospective re-evaluation of a routine invasive strategy following successful thrombolysis.

The technical developments in interventional cardiology in the past decade and the use of glycoprotein IIB/IIIA receptor blockers will certainly contribute to a reduction in procedure-related events (25). After balloon angioplasty following successful thrombolysis, reocclusion is still frequent (~17%) (24), with an incorporated risk for reinfarction. This underscores the need for stenting. The use of intravascular ultrasound may further improve procedural outcome and provide more detailed information for identification and characterization of the culprit lesion (26). Although this was not confirmed in our study, previous angiographic studies showed an association between complex morphology of the culprit lesion and impaired outcome in patients with unstable angina (27).

Furthermore, our findings suggest that the routine invasive arm of a future trial should not prescribe a certain cutpoint for severity of the culprit lesion to perform angioplasty. Many of the past randomized trials used a visually assessed stenosis severity of 60% or 70% as cutpoint (13). Our observations suggest that reocclusion of a lower grade lesion, proportionally, more often occurs symptomatically than reocclusion of a more severe lesion.

After several non-randomized reports suggesting favorable outcome with routine angioplasty after thrombolysis (28,29), the randomized GRACIA-trial recently showed that in the current era routine revascularization following thrombolysis is safe and feasible (30). Low event rates precluded conclusions with respect to clinical outcome. Importantly, with the benefit of a routine invasive approach being uncertain as of to date, an active approach of viability and ischemia detection is mandatory.

Given the favorable outcome after successful thrombolysis large patient numbers and long-term follow-up are required for a clinical efficacy study. However, in the

case of stunned or hibernating myocardium improving and/or maintaining infarct artery patency could result in left ventricular contractile recovery (31). A primary angiographic endpoint could therefore also be considered, i.e. the incidence of reocclusion or improvement in left ventricular ejection fraction.

Study limitations

Our findings refer to a rather selected studypopulation of clinically stable patients younger than 71 years, who received thrombolysis within 4 hours of symptom-onset and showed clinical and/or electrocardiographic signs of reperfusion with angiographically proven patency at 24-hour angiography. This may explain the low event rates in our study. However, the substantial reocclusion rates confidently allow comparison of the proportion of asymptomatic reocclusions between patients with a high-grade and a low-medium-grade residual stenosis.

Despite careful identification of the culprit lesions by the angiographic committee, we can not exclude that misinterpretations may have occurred, especially in patients with multi-vessel disease and multiple lesions.

Although patients were screened regarding history and ECG for silent reinfarction, it cannot be excluded that patients with a high-grade lesion experienced more silent reinfarctions.

Whereas to date use of the TIMI criteria (22) is standard in angiographic studies, the APRICOT-1 trial used the ECSG criteria (2). If only anatomical reocclusions – ECSG grade 5 stenoses (2) - were considered, the outcome of this analysis would not change.

Conclusion

Even though our observations should be considered as hypothesis generating, they challenge the generally believed association between a high-grade stenosis and reinfarction in patients with an open infarct artery after thrombolytic therapy. This was observed in the setting of a rather conservative, ischemia-guided revascularization strategy. In addition to peri-procedural events, the fact that past trials on routine angioplasty mainly focused on severe lesions may also explain their lack of clinical benefit. Our findings indicate that reocclusion of a lower grade lesion is more likely to result in clinical reinfarction.

Based on these findings, a future randomized re-evaluation of a routine invasive strategy should target all amenable lesions, using glycoprotein IIb/IIIa blockers and stents to reduce peri-procedural events and reocclusion.

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CHAPTER 10

Sustained coronary patency after fibrinolytic therapy as independent predictor of 10-year cardiac survival

Observations from the APRICOT-trial

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Abstract

Background: Reocclusion is seen in about 25-30% of patients within the first year after successful fibrinolysis, and often occurs in the absence of clinical reinfarction. Most reinfarctions occur early after fibrinolysis and carry a twofold increased risk of mortality. Notably, even in the absence of clinical reinfarction, reocclusion has been shown to impair left ventricular contractile recovery. The prognostic consequence of late reocclusion has not been thoroughly addressed. We therefore assessed the impact of 3-month coronary patency on 10-year cardiac survival, and if an effect independent of left ventricular function could be demonstrated.

Methods and Results: In the ischemia-guided APRICOT-1 trial 248 ST-elevation MI patients with an open infarct artery 24 hours after fibrinolysis had 3-month repeat angiography to assess reocclusion. In 99.6% of surviving patients > 10 years of clinical follow-up was available. Reocclusion was observed in 71 of the 248 patients (29%). Cardiac survival at 10 years was 88% for patients with sustained patency and 73% in patients with a reoccluded infarct artery ($p < 0.01$), a difference also present in patients without ischemic symptoms between angiograms (85% versus 73%; $p < 0.03$). Multivariable analysis identified sustained patency at 3-month angiography as independent predictor of 10-year cardiac survival (HR 2.10; 95%CI 1.10 - 4.02) together with left ventricular ejection fraction.

Conclusions: Sustained infarct artery patency in the 3 months after fibrinolysis is a strong predictor of 10-year cardiac survival, independent of left ventricular function. Given the detrimental impact of both symptomatic and asymptomatic reocclusion, future preventive strategies should also focus on 'clinically silent' reocclusions. Studies on better antithrombotic regimens and their combination with a routine invasive strategy at some time point after fibrinolysis are warranted.

Introduction

Despite a gradual increase in the use of primary percutaneous coronary interventions for ST-elevation myocardial infarction, the majority of patients is still treated with fibrinolytic therapy. Unfortunately, part of the initial success of pharmacological reperfusion is offset by reinfarction, recurrent ischemia and reocclusion (1). The incidence of 30-day reinfarction is about 5%, half of which occurs within 48 hours after fibrinolysis (2), often attributable to infarct artery reocclusion. These early symptomatic reocclusions are associated with a twofold increase in mortality (1,2,3).

Reocclusion rates increase from 5 to 10% before discharge (1,4,5) to about 20 to 30% in the 3-12 months after fibrinolysis (6,7,8). Systematic angiographic follow-up has revealed that about half of reocclusions occurs without overt ischemic symptoms (9,10). Interestingly, even when reocclusion occurs in the absence of clinical reinfarction, impaired left ventricular contractile recovery has been demonstrated (11). In contrast, patients with sustained patency showed improvement in left ventricular ejection fraction, a key correlate of both short- and long-term outcome (12).

To date only one study after fibrinolysis demonstrated the adverse prognostic consequences of late reocclusion over a 6-year follow-up period, independent of left ventricular function. Reocclusion was assessed 6 months after routine angioplasty, performed 10 days after fibrinolysis (10). Other studies on the impact of an open artery reported contradicting findings, and included a heterogeneous population of patients with persistently occluded and reoccluded infarct arteries, both with and without prior reperfusion therapy (13).

In light of the renewed interest in the concept of late coronary patency (13), we studied the impact of 3-month coronary patency on 10-year cardiac survival, adjusted for left ventricular ejection fraction, in a well defined population of myocardial infarction patients with a patent infarct artery 24 hours after fibrinolysis, in whom an ischemia-guided revascularization strategy was followed.

Methods

Protocol

The APRICOT-1 study protocol has been reported in detail previously (6). In brief, 300 patients < 71 years old with chest pain lasting > 30 minutes and < 4 hours, and 0.2 mV ST-segment elevation in at least 2 contiguous leads on the electrocardiogram (ECG), received fibrinolysis for suspected myocardial infarction followed by 20,000 U of intravenous heparin/24h. In the case of clinical and/or electrocardiographic signs of reperfusion, clinically stable patients were asked informed consent to undergo coronary angiography within 48 hours after fibrinolysis. Patients with a patent infarct artery, defined as grade 1 to 3 stenosis according to the European Cooperative Study Group (ECSG) criteria (Table I), were eligible for the study. Sixteen patients were retrospectively excluded for not having a patent infarct artery at baseline angiography according to the blinded angiography committee.

The 284 patients with a patent infarct artery were randomly allocated to one of three arms: blinded treatment with either 325 mg of aspirin or placebo, or open-label coumadin including continued heparinization until the target INR (2.8-4.0) was reached. Symptom-limited bicycle stress testing according to the local hospitals' protocol was performed at discharge or before the first out patient visit, planned at 4-6 weeks after admission. By protocol, revascularization was only to be performed for recurrent ischemia refractory to maximal anti-ischemic medication.

Cardiac catheterization

Follow-up angiography was scheduled at three months to assess reocclusion, defined as a grade 4 or 5 stenosis. If coronary angioplasty was performed before the planned repeat angiography, the patency status of the infarct artery before dilatation was scored as follow-up endpoint.

Left ventricular ejection fraction was calculated from the 30^0 right anterior oblique ventriculogram by the area-length method. One of the participating centers did not routinely perform ventriculography. In 36 cases ejection fractions at angiographic follow-up were not available. In 15 of these data were retrieved and/or retrospectively assessed (M.B./F.W.A.V.); information from the medical chart and ejection fractions determined otherwise (echocardiography, nuclear imaging) were used in the case angiograms were not available and/or angiographic ejection fraction data were not reported.

Clinical follow-up

Ten-year survival data were collected from medical charts, municipal registries, or by telephone contact with the patient, relatives or the general practitioner. Cardiac mortality was defined based on the information of the treating physician, and only in the case of a confirmed cardiac diagnosis. An instantaneous death, for which the cause could not be determined with certainty, was scored as a death of cardiac origin.
Confirmed vascular deaths (strokes, aneurysms, dissections, pulmonary embolisms) were not considered as cardiac death. If the cause was unknown/uncertain and death did not occur instantaneously it was classified as 'cause undetermined'.

Statistics

Statistical analysis was performed with SPSS 11.0 (SPSS Inc. 2001, Chicago, USA). Differences between continuous variables were compared using the Student's t-test and Mann-Whitney-U-test whenever appropriate. Comparisons of proportions between groups were performed with the χ^2-test. Statistical significance was defined as a two-sided p-value < 0.05.
Long-term survival analysis was performed according to Kaplan and Meier, using the log-rank test for a univariate comparison between patients with coronary patency at follow-up angiography and those with a reoccluded infarct artery.
Multivariable Cox-regression analysis using forward logistic regression was used to determine the association between infarct artery patency at follow-up angiography and 10-year cardiac survival. Variables studied were baseline characteristics that were imbalanced between the study groups ($p < 0.10$, see Results) and variables with a univariate association with 10-year cardiac survival ($p < 0.10$, see Results). Infarct artery, left ventricular function and age were prospectively chosen to be included, irrespective of the corresponding p-value.

Table 1 European Cooperative Study Group classification

Stenosis grade	
0	Normal
1	< 50% diameter stenosis
2	50% to 90% diameter stenosis
3	91% to 99% diameter stenosis, complete filling within 3 cycles
4	91% to 99% diameter stenosis, no complete filling within 3 cycles
5	Total occlusion with or without collateral filling

Results

Of the 284 patients who had a patent infarct artery 24 ± 14 hours after fibrinolytic therapy, 248 (87%) underwent follow-up angiography performed 75 ± 31 days later. Refusal to undergo the second angiography was reported in 28 of 36 cases; two patients died and the other six patients had coronary bypass surgery. Patients without follow-up angiography were more often female (31% vs. 17%, $p < 0.05$), older (60 ± 7 vs. 56 ± 9 years, $p < 0.01$) and more often had a history of myocardial infarction (17% vs. 6%, $p < 0.03$).

Reocclusion was observed in 29% of patients, dividing the present study population in 71 with reocclusion and 177 with sustained infarct artery patency at follow-up angiography. During follow-up a total number of 59 deaths was observed, 40 of which were cardiac, 18 were non-cardiac and 1 was unclassifiable (in the group with sustained patency). In all but one of the surviving patients more than 10-year follow-up was available (99.6%). In total, clinical follow-up was available for 9.0 ± 2.4 years, without a difference between groups. Baseline characteristics of both groups are presented in Table 2.

Infarct artery patency and cardiac survival

Overall, 21 deaths were observed in the reocclusion group, and 38 in the group with sustained patency. All-cause 10-year survival did not differ significantly: 70% vs. 79% ($p = 0.16$). Cardiac 10-year survival rates were lower in patients with reocclusion: 73% versus 88%, respectively (Fig. 1, log-rank $p < 0.01$). Table 3 shows the impact of reocclusion according to infarct location and left ventricular function. Also in the case of infarctions related to the right coronary artery, a marked difference in cardiac survival was observed: 77% vs. 91% ($p=0.06$). The negative prognostic impact of reocclusion was observed both in patients with and in those without an ejection fraction < 40%. Also in the case of an ejection fraction ≥ 50% this adverse effect was apparent: 10-year cardiac survival was 76% in those with reocclusion (n=38) and 90% in patients with sustained patency (n=107; $p < 0.05$).

Of the 71 patients with reocclusion 33 (47%) were asymptomatic between angiograms (no reinfarction, unstable angina, or angina with positive stress testing). Their 10-year cardiac survival rate was 73% as compared to 85% for the asymptomatic patients with an open infarct artery (Fig. 2, log-rank $p < 0.03$).

Revascularizations

In 14 patients reocclusion was detected due to clinically driven angiography, before the scheduled 3-month angiography. In all angioplasty was performed, which was unsuccessful in two. One of these patients was successfully revascularized with a subsequent CABG.

In 12 patients from the group with sustained patency angiography was performed earlier than scheduled. In all angioplasty was performed. Two procedures were unsuccessful, and one was followed by a CABG resulting in a successful revascularization.

If these patients were analyzed according to the status of the infarct artery after the revascularization (CABG = restored patency), the respective 10-year cardiac survival rates would have been 72% for the "reocclusion" group (n=59) and 87% for the group with "sustained/restored patency" ($p = 0.01$).

Prognostic impact of infarct artery patency and left ventricular function

By univariate comparison age, previous myocardial infarction, multivessel disease and a left ventricular ejection fraction tended to be associated with lower 10-year cardiac survival (Table 4).

These variables were studied in a multivariable Cox-regression model including infarct artery patency and infarct artery at angiographic follow-up. Forward logistic regression analysis identified reocclusion as predictor of 10-year cardiac death (HR 2.10; 95%CI 1.10 - 4.02), independent of left ventricular function, which turned out as the only other independent prognostic variable (Table 5). When including ejection fraction as dichotomous variable, the corresponding hazard ratios for 10-year cardiac death were 2.18 (95%CI 1.14 - 4.17) for reocclusion and 2.10 (95%CI 0.99 - 4.47) for an ejection fraction < 40%.

Table 2 Clinical and angiographic characteristics at 3-month angiography

	Sustained Patency n = 177	**Reocclusion n = 71**
Men	138 (81%)	62 (87%)
Age (years)	56 ± 9	57 ± 9
History of MI*	11 (6%)	4 (6%)
Antithrombotic therapy:		
Aspirin	70 (40%)	23 (32%)
Coumadin	57 (32%)	24 (34%)
Placebo	50 (28%)	24 (34%)
Clinical status:		
Symptomatic	32 (18%)	38 (53%)
Asymptomatic	145 (82%)	33 (47%)
Infarct-related artery:		
LAD	71 (40%)	34 (48%)
LCX	28 (16%)	11 (15%)
RCA	78 (44%)	26 (37%)
Single vessel disease	106 (60%)	36 (51%)
Ejection fraction%	55 ± 11 (n=158)	51 ± 12 (n=69)
≤ 40%	17 (11%)	14 (20%)
≤ 50%	51 (32%)	31 (45%)

Data are presented as the number (%) of subjects for discrete variables, and as mean ± SD for continuous variables

* Not including the index infarction related to inclusion in APRICOT-trial

MI = myocardial infarction; LAD = left anterior descending artery; LCX = left circumflex coronary artery; RCA = right coronary artery

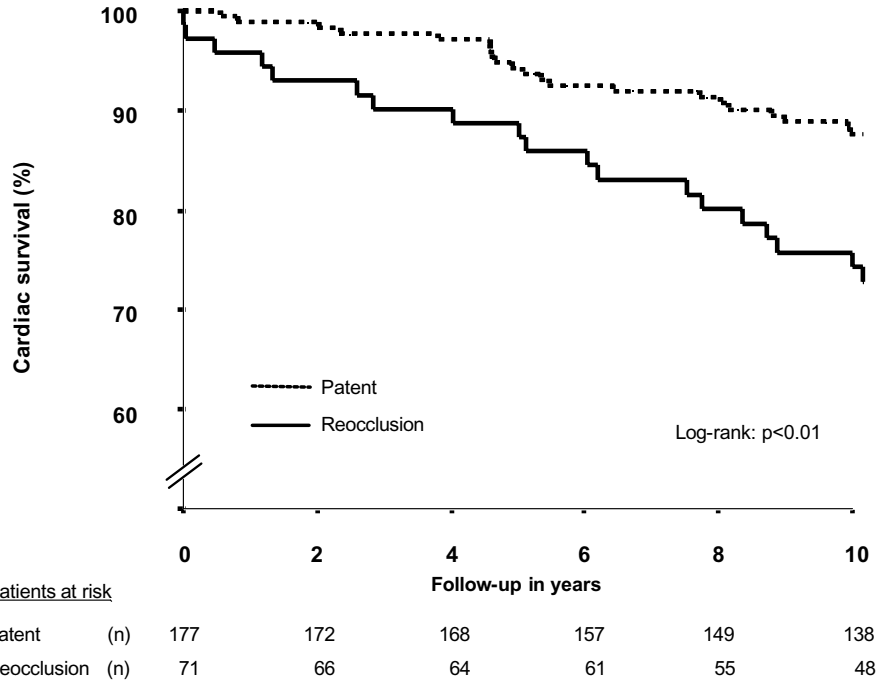

Figure 1: Impact of reocclusion on 10-year cardiac survival after fibrinolysis for ST-elevation myocardial infarction.

Table 3 Prognostic impact of late coronary patency for infarct site and left ventricular function

Coronary patency and 10-year cardiac survival in subgroups				
Variable	**Patency (n = 177)**	**Reocclusion (n=71)**	**p Value**	**Interaction-p**
Infarct Artery				
LAD (n=105)	85%	68%	0.03	ns
nonLAD (n=143)	89%	78%	0.09	
Left (n=144)	85%	71%	0.04	ns
Right (n=104)	91%	77%	0.06	
Ejection Fraction				
≤ 40% (n=31)	82%	57%	0.08	ns
> 40% (n=196)	88%	78%	0.08	

Survival percentages as determined by Kaplan and Meier, compared by log-rank.
LAD = left anterior descending artery; Left= LAD and left circumflex coronary artery;
Right = right coronary artery

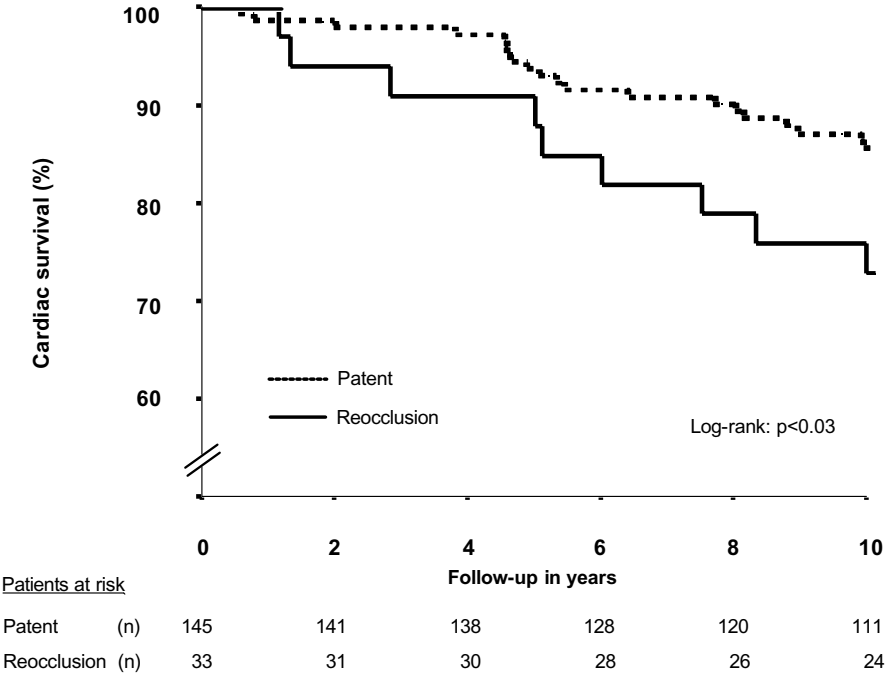

Figure 2: Impact of reocclusion on 10-year cardiac survival after fibrinolysis in patients without ischemic symptoms at the time of angiographic follow-up.

Table 4 Univariate associations with 10-year cardiac death

	Cardiac death (n = 40)	No cardiac death (n = 208)	p Value
Age (years)	58 ± 9	56 ± 9	0.09
Previous MI	13%	5%	0.02
Multivessel disease	55%	40%	0.06
Infarct Artery			
LAD	53%	40%	0.13
Left	68%	56%	0.16
Ejection Fraction (%)	50 ± 14 (n = 37)	55 ± 11 (n = 190)	0.05
≤ 40%	24% (n = 9)	12% (n = 22)	0.08
≤ 50%	49% (n = 18)	34% (n = 64)	0.10

LAD = left anterior descending artery; Left= LAD and left circumflex coronary artery
MI = myocardial infarction

Table 5 Independent predictors of 10-year cardiac death

	Hazard Ratio	**95% CI**	**p Value**
Age per year	1.04	0.99 - 1.08	0.06
Ejection Fraction % (continuous)	0.97	0.94 - 0.99	0.03
Reocclusion	2.10	1.10 - 4.02	0.03

Discussion

This 10-year clinical follow-up report on 248 ST-elevation myocardial infarction patients shows that reocclusion in the subsequent 3 months after fibrinolysis is an important predictor of long-term cardiac mortality, independent of left ventricular function, even in a rather low-risk population of patients.

Late infarct artery patency and long-term survival

Although the prognostic consequences of early infarct artery patency (5) and early reinfarction and reocclusion are undisputed (1-3), conflicting data have been reported regarding the independent impact of late coronary patency (13). Part of this may be related to the fact that single angiogram observations studied mixed populations of patients, with either persistently occluded or reoccluded arteries, with or without prior reperfusion therapy. When restricted to patients after reperfusion therapy, data corroborate well, supporting the concept of late patency (9,10,14-16). Importantly, these studies often had paired angiography (9,10,16) and reflected the impact of sustained patency versus reocclusion.

The first study after fibrinolysis that showed an independent relationship between late reocclusion and long-term mortality described consecutive patients who underwent routine angioplasty about 10 days after fibrinolysis, with reocclusion detected at 6-month angiographic follow-up (10). In the APRICOT study a rather conservative, ischemia-guided revascularization strategy was adopted, with an overall 3-month revascularization rate of only 11%. The present findings therefore merely reflect the 'natural course' after fibrinolysis. Extension of our 3-year follow-up report shows that reocclusion is not only associated with increased rates of reinfarction and revascularization (9), but also with 10-year cardiac mortality. Also after primary angioplasty reocclusion has been reported to have independent prognostic impact (16), but observational evidence suggests that with the introduction of stenting reocclusion is a rather infrequent phenomenon (~6%) (17).

In all three studies, with different reperfusion and subsequent revascularization strategies, reocclusion increased mortality by factor 2, with the most pronounced effects in patients with anterior infarction and/or impaired left ventricular function (10,16). Its adverse impact has now been reconfirmed for patients with good ejection fractions ($\geq$ 50%) after fibrinolysis (10) and extends to patients with right coronary artery infarctions in the present report.

Adverse consequences of reocclusion for left ventricular function have been noted in all studies (6,10,11,16). Although the deleterious impact of clinical reinfarction is well-established, our group demonstrated impaired left ventricular recovery even when reocclusion occurs in the absence of clinical reinfarction (11). Moreover, we demonstrated an increased risk for ventricular dilatation during 5-year echocardiographic follow-up (18). Interestingly, both observations after fibrinolysis show that at least half of reocclusions occur without ischemic symptoms (9,10), and the present analysis underscores the adverse impact of these clinically silent reocclusions. Even in patients without ischemic symptoms in the 3 months after fibrinolysis, and with reocclusion being merely detected as a result of the systematic angiographic follow-up, 10-year cardiac survival was adversely affected.

As of to date, new treatment regimens have primarily aimed at a reduction in the incidence of reinfarction, but our findings underscore the need to expand our focus toward predictors of these 'silent' reocclusions and corresponding preventive strategies.

Prevention of reinfarction and reocclusion: antithrombotic strategies

With the role of aspirin being undisputed after fibrinolytic therapy (19), several alternatives to unfractionated heparin have been tested, such as low-molecular weight heparins, the specific Xa inhibitor pentasaccharide and the direct thrombin inhibitor hirudin (20-24).

Although all randomized comparisons reported reduced reinfarction rates on the new agents (20,22,23), only hirudin was administered for a similar duration as unfractionated heparin (24). The other new antithrombotics were often given until discharge, reducing reinfarction rates during treatment, but with a catch up phenomenon after discontinuation (20,22).

The angiographic trials showed higher patency rates at discharge after prolonged anticoagulation with the new agents when compared to a regimen of 48-72 hours of unfractionated heparin (21,22,23). These clinical and angiographic observations suggest that to prevent reinfarction and to improve patency rates a prolonged antithrombotic regimen is mandatory.

The results of the APRICOT-2 trial support this hypothesis with a 40-50% reduction in 3-month reocclusion after a prolonged, combined antithrombotic regimen (8). Now that several clinical trials have demonstrated a benefit of the combination of aspirin with medium-high intensity oral anticoagulation (25), oral thrombin inhibitors (26) may become a practical alternative.

As far as additional anti-platelet therapy to aspirin is concerned, the currently running CSS-2 trial and the CLARITY-TIMI 28 trial study the impact of the adjunctive use of clopidogrel on clinical outcome and predischarge coronary patency, respectively.

Prevention of reinfarction and reocclusion: revascularization strategies

With stenosis severity being one of the few variables consistently reported to be associated with reocclusion (1,4,28), more aggressive revascularization strategies early after fibrinolysis have been tested. These studies primarily addressed the prevention of reinfarction, and did not assess reocclusion. Most trials were performed a decade ago, and a routine invasive strategy after successful fibrinolysis did not improve clinical outcome, mainly due to high peri-procedural event rates (29). These studies do not represent modern cardiology with improved angioplasty techniques, stenting and the protective effect of concomitant use of glycoprotein IIb/IIIa receptor blockers. The GRACIA-1 trial re-evaluated the safety and feasibility of a modern routine invasive strategy within 24 hours after fibrinolysis, though not restricted to patients with open infarct arteries, and reported higher patency rates and improved left ventricular function at one year (30). Larger trials and long-term follow-up are needed to substantiate conclusions regarding the clinical benefit.

Systematic angiography and subsequent elective intervention before discharge seems another promising revascularization regimen after ST-elevation MI. In stable patients with one vessel disease recurrent angina was reduced, and 5-year follow-up suggested a positive effect on survival when compared to standard medical care (31). Reocclusion was not studied, but sustained infarct artery patency after angioplasty and stenting may hypothetically have contributed to the observed clinical outcomes.

Late opening of (re)occluded arteries

Although prevention of reocclusion is to be preferred, late recanalization has become a new challenge given the improvements in the field of interventional cardiology (13). Several potential mechanisms of benefit have been implicated, varying from better electrical stability, the possibility of collateral supply to another coronary territory and assumed beneficial effects on left ventricular function (32).

When confronted with an occluded infarct artery at some time point after reperfusion therapy it is difficult to differentiate between a persistently occluded

and a reoccluded artery. In view of the adverse impact of coronary (re)occlusion, reopening might exert a positive effect. Notwithstanding the hypothetical advantages of prevention of reocclusion, and of recanalization after reocclusion, it should be realized that reocclusion could only be a marker of poor prognosis, and not have a direct causal relationship with outcome.

The randomized trials on late recanalization have so far been underpowered for clinical endpoints. Unexpectedly, routine recanalization about 1 month after fibrinolysis resulted in a higher incidence of ventricular dilatation (33). In the prematurely discontinued DECOPI study (34), 6-month-patency after myocardial infarction was significantly better after the invasive strategy (83% vs. 40%), as was ejection fraction (43.5% vs. 40.0%). The currently running Occluded Artery Trial (OAT) will be the first properly sized randomized trial to address the clinical impact of late recanalization (13).

Limitations

Although the present study population was well defined (all fibrinolysis, open infarct artery, participating in angiographic follow-up trial) they form a rather selected group of low-risk patients (7). The cardiovascular risk profile and medication were not routinely scored during follow-up, and thus, differences between groups can not be excluded. Finally, the low mortality rate and relatively modest sample size reduced the power of subgroup analyses.

Conclusions and implications

The present report fuels the interest in the concept that late infarct artery patency is an important prognostic factor for long-term cardiac mortality after ST-elevation myocardial infarction, independent of left ventricular function. Whereas many of the previous trials addressed mixed populations of patients with persistently occluded and reoccluded infarct arteries, the APRICOT-trial describes the impact of sustained infarct artery patency in the 3 months after fibrinolytic therapy. In view of the profound clinical consequences, future strategies should focus on the prevention of not only symptomatic, but also asymptomatic reocclusion. A combination of more intensive antithrombotic regimens and a more aggressive revascularization strategy, with routine stenting and including late recanalizations, should become the platform for future research.

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PART 3 Perspective

CHAPTER 11

Epicrise and Summary

Epicrise

This thesis has covered various elements in the antithrombotic treatment of acute ST-elevation myocardial infarction. We tried to demonstrate the potential of angiographic follow-up studies and of trials with long-term clinical follow-up to gain further insights with regard to the treatment of ST-elevation myocardial infarction.

The reported observations such as reocclusion in the absence of overt clinical symptoms, and its potential prognostic impact, emphasize the importance of mechanistic studies initiated by clinicians themselves. The presently more and more common routine seems to expeditiously conduct large scale trials, often industry-initiated, comparing two agents or strategies and restricted to clinical endpoint comparisons at 4-5 weeks after infarction. Perhaps under pressure of competing firms, it has even occurred that angiographic pilot trials were published later than the subsequent clinical trial.

In contrast, the renowned GUSTO-1 trial has offered unique insights in our understanding of the treatment, risk-stratification and several pathophysiological concepts in ST-elevation myocardial infarction, as it incorporated both a comparison on clinical endpoints, including long-term follow-up, and an angiographic substudy.

In the studies reported in this thesis, the university and clinicians initiated the projects, using antithrombotic regimens of which the potential consequences for the industry sharply contrast with the previously mentioned studies. However, both in the field of reperfusion therapy, and with regard to the prevention of recurrent thrombotic events, either with antithrombotic agents or by a more aggressive revascularization strategy, our observations have provided additional information that may affect future research and further improve clinical practice.

Improvements in the field of reperfusion therapy

Chapter 2 and 3. With the demonstration that 90-minute TIMI grade 3 flow was strongly correlated with outcome, many new fibrinolytics have been developed, which have all been tested in a moderately sized angiographic trial before a clinical trial was undertaken. Unfortunately, the recent large scale clinical trials did not incorporate an angiographic substudy to validate the hypotheses based upon

the results of the pilot studies. Although various agents with higher angiographic patency were tested, mortality rates did not improve. The lack of systematically performed angiographic, electrocardiographic and laboratory substudies has precluded a thorough analysis for explanations of these findings.

Perhaps blinded in search of newer, more potent pharmacological agents several basic guidelines have not been applied to practice to its full extent. Many patients that meet the criteria for reperfusion therapy (fibrinolysis/primary PCI) are not treated accordingly. In addition, in-hospital treatment delays are still often trivialized, and the potential impact of reducing treatment times is often underestimated. In analogy, it has taken over years for prehospital fibrinolysis programs to be implemented on a larger scale.

The MITI trial is one of the best examples that even in the United States of America, with a rather strict system of law, these initiatives can be implemented successfully. It is often not realized that quantitative review of all randomized trials has demonstrated that about 16-18 lives can be saved per 1000 patients treated in the ambulance when compared to in-hospital initiation of treatment. These numbers are in the same order of magnitude as the benefit achieved by performing primary angioplasty in stead of in- hospital fibrinolysis.

Head to head comparisons between prehospital fibrinolysis and primary angioplasty are scarce, and the single randomized trial, which was unfortunately prematurely discontinued, reported no difference in outcome. In this trial, a rather liberal policy of rescue angioplasty was adopted after fibrinolysis. These findings warrant further investigation, given the profound implications this might have for the currently existing logistic problems to meet the increasing need for primary angioplasty. With reocclusion and reinfarction being more frequent after a rather conservative revascularization strategy after pharmacological reperfusion therapy, future comparisons to a primary PCI should adopt a liberal intervention strategy after pharmacological reperfusion therapy.

Now that time to treatment has also been proven of importance for primary angioplasty, and outcome of the procedure has been shown to be dependent of preprocedural TIMI grade flow, the concept of facilitated percutaneous intervention has been introduced. Appreciating that prehospital fibrinolysis results in an hour time gain, and that door-to-balloon times of 60-90 minutes are common practice, a combination of prehospital fibrinolysis with subsequent intervention might be the optimal pact between pharmalogical and mechanical reperfusion therapy. Several

studies with different forms of pretreatment (fibrinolyis, glycoprotein IIb/IIIa receptor blockers or a combination of both) have been initiated to test this concept.
Based on these premises, the design of a randomized trial comparing two reperfusion strategies in the Nijmegen area is currently under investigation. In patients with large infarctions (cumulative ST-deviation of 15 mm or more) prehospital randomization is planned after administration of aspirin and heparin to either 1. primary angioplasty or 2. fibrinolysis with a subsequent clinically driven intervention.

Need for better adjunctive antithrombotic strategies

Chapter 2, 4, 6,7 and 9. Although early realization of brisk, antegrade coronary flow forms a main priority in the acute phase, maintaining an open infarct artery afterwards is crucial: Early reinfarction and reocclusion increase the risk of mortality by factor 2. Until now, the efficacy of new antithrombotic regimens has always been expressed in terms of a reduction in death and reinfarction. With the improvements made over the years, the rate of this combined endpoint has been markedly reduced and large sample sizes are required to demonstrate significant improvements. Incorporation of reocclusion as an endpoint, and studying a restricted, but better defined population may tackle part of this problem.
Notably, this requires paired angiography, and to study reocclusion randomization will have to take place after TIMI grade 3 flow in the infarct artery has been demonstrated. Given its incidence of 7-10% at the time of discharge and 20-30% in the 3 months after myocardial infarction, studies could be markedly reduced in sample size when considering 30-day reinfarction rates of 4-5%. Appreciating the adverse effects on left ventricular function, this could also be assessed as an 'indirect' endpoint given its potential impact on late survival. For further validation, subsequent long-term clinical follow-up could be performed.
If follow-up angiography is considered practically difficult, a second possibility is to restrict comparisons of new antithrombotic regimens to patients in whom reinfarction is more likely to occur, for example those with electrocardiographic signs of reperfusion and demonstrated viability in the infarct area. In the recently performed studies large numbers of patients had to be included, because much of the potential reductions of new agents on recurrent thrombotic events is diluted either due to a considerable proportion of patients in whom reperfusion is not achieved, or to a lack of viable myocardium in the area supplied by the infarct artery.

These strategies may allow moderately sized studies to give a first impression as to the potential of new antithrombotic agents. Another aspect that deserves more thorough investigation as compared to recently introduced agents concerns the kinetics of the new agents, especially in the elderly and patients with impaired renal function. Subsequently, larger scaled clinical trials, with angiographic and laboratory substudies could be restricted to the agents that showed promising findings in the smaller, more conceptual studies.

Another important aspect concerns the duration of the compared antithrombotic regimens, and the definition of the outcome measure used. As of to date, no convincing evidence has been published that low-molecular weight heparins are more potent than unfractionated heparin. The perception that these agents are superior is caused by two factors. First, the new agents were administered until discharge, as compared to 48-72 hours of unfractionated heparin. Second, the primary endpoint of the trials did not always incorporate reinfarctions occurring after discharge. If these are taken into account a catch-up phenomenon after discontinuation is observed for patients on the low-molecular-weight heparins.

For the design and interpretation of future trials, these factors should be taken into account. Moreover, more laboratory substudies are warranted to further elucidate the complex interplay of the coagulation factors, platelet activation and their association with future events.

In line with the observations from APRICOT that recurrent thrombotic events and reocclusion are still frequent after successful fibrinolysis, one of our future projects will address the issue of 'aspirin resistance'. Despite a marked 20% relative risk reduction as result of the introduction of this agent after acute coronary syndromes, four out of five recurrent events are still not prevented. The prediction of which patients are at increased risk of subsequent events, and the insight into the underlying pathophysiological mechanism can still be futher improved.

The Study on Asprin Resistance in major Antithrombotic (SARA) trials has been designed to further unravel pathophysiological, clinical and angiographic aspects, and to come to a more sound definition of this rather ill-defined phenomenon.

Routine vs. ischemia-guided revascularizations

Chapter 8. Although previous studies on a routine invasive strategy did not result in better outcomes than an ischemia-guided approach, a re-evaluation in the current

era of improved interventional techniques is awaited. Periprocedural events can now be reduced by as much as 50% with the concomitant use of glycoprotein IIb/IIIa receptor blockers, and equipment has improved. With the observations from ischemia guided angiographic follow-up studies that reinfarction may not be predicted by the severity of the residual lesion, a mere re-do of the previous trials seems too restricted. In these studies death and reinfarction were the primary endpoint(s), which are relatively infrequent after successful fibrinolysis. Moreover, angioplasty was often not performed in the case of intermediate residual lesions.
Angiographic patency at some time point, or, preferably, reocclusion should be incorporated as (part of the) endpoint, as well as left ventricular function. It remains to be determined whether the expected benefits of such a strategy of routine revascularization outweigh the also incorporated procedural risks. Irrespective of the outcome of the trials, they will provide insight into which patients are at increased risk for periprocedural events in the current era of improved interventional techniques. In the case a routine invasive strategy may not prove beneficial, these data may allow a risk-benefit stratification which could form the basis for a future, elective, risk stratified invasive approach.
The APRICOT-3 trial will be a mechanistic, angiographic study addressing the impact of a routine invasive approach after successful fibrinolysis. Patients with an open infarct artery after fibrinolysis will be randomized to a routine invasive strategy or an ischemia-guided approach. Reocclusion and left ventricular function will be the primary outcome measures, and long-term clinical follow-up will be collected.

From angiography to clinical practice

Despite the abovementioned advantages of performing angiographic (sub)studies, it is important to realize that this type of research requires specialist knowledge and experience, not only because of the (small) chance of complications, but also with respect to the design and organization of such a study.
The type of studyquestion also determines whether angiography is an appropriate method to get a first impression of a given intervention. As has been demonstrated in this thesis, studies regarding the influence of interventions on (sub)total coronary (re)occlusions after ST-elevation myocardial infarction and its impact on prognosis can be reliably performed provided the implementation of a sound methodology.

Studies describing the impact on the more subtle changes of coronary artery disease progression are more difficult to interpret, partly because of the limititations inherent to angiography to detect these changes.

In addition, the timing of the second angiography is crucial when recurrent coronary thrombosis is studied. If repeat angiography is performed at a standard time, valuable information could be lost in patients with a recurrent ischemic event before the scheduled angiography. In these patients, the second angiography should be performed at the time of the event, or as early as possible afterwards to detect a possible coronary (re)thrombosis. Unfortunately, only a few studies follow this policy. Various medical interventions (ACE-inhibitor, poly-unsaturated acids) that proved cardioprotective in clinical trials did not show a reduction in coronary thrombosis in the angiographic trials, probably partly caused by the timing of the follow-up angiography. Even prothrombotic agents such as hormone replacement therapies were not identified as such in the angiographic trials. It is therefore of the utmost importance to carefully consider the study population, the type of intervention tested, and the expected effects in the consideration to perform an angiographic (follow-up) study. Subsequently, hypothesis testing is required in large scale clinical trials.

If the above mentioned elements are carefully considered, and the study is performed by an experienced research group, angiographic (sub)studies can certainly contribute to comparisons of interventions, improvement of our understanding of underlying pathophysiological mechanisms, and refinement of postinfarction risk stratification to come to a more individualized treatment of patients after myocardial infarction.

In view of the above, it can be concluded that with the development of three lines of research new opportunities have been created towards the further improvement of the treatment after myocardial infarction, based on the insights that will be obtained through conduction of these projects. Appreciating that not all treatments are as successful for everyone, and that both with respect to efficacy and safety different risk-benefit profiles should be distinguished for each patient individually, our search should be aimed at a more individualized approach. In anticipation, the design and protocol of future research will have to be designed accordingly, to start and provide a sound background to support and optimize such an approach in daily clinical practice.

Summary

After a general introduction in **Chapter 1** explaining some basic background information with respect to acute coronary syndromes and more specific terms used throughout the manuscript, the outline of the thesis forms a concise description of the study questions and briefly addresses their clinical and scientific impact.

Chapter 2 describes the current standard of care for the pharmacological treatment of acute ST-elevation myocardial infarction. Moreover, it forms a brief review of the history of developments in this field and provides insight into the pathophysiological rationale of these new treatment regimens.
Reperfusion therapy. Despite a strong relationship between 90-minute TIMI-grade 3 flow and 30-day mortality, new reperfusion regimens with higher patency rates did not result in improved survival. An example forms the combination of half-dose lytic with full-dose glycoprotein IIb/IIIa receptor blocker therapy. Moreover, this regimen was expected to reduce bleeding rates, intracranial hemorrhage in particular, but resulted in increased intracranial bleeding in the elderly, whereas in the younger patients the expected reduction was observed.
Adjunctive antithrombotics. New anticoagulant therapies that were tested against unfractionated heparin after fibrinolysis seemed to do better in the prevention of reinfarction and recurrent ischemia, and were therefore often reported to be superior to unfractionated heparin. In fact, a strategy of prolonged anticoagulation until discharge with the new agents resulted in better outcomes when compared to 48-72 hours of intravenous unfractionated heparin. With a 'catch-up phenomenon' after discontinuation of the new agents, 30-day and 1-year reinfarction rates were similar to those after unfractionated heparin. Only with hirudin, administered for a similar duration as unfractionated heparin, 30-day reinfarction rates have been reduced after fibrinolysis with streptokinase. Angiographic studies after fibrinolysis showed comparable 90-minute patency to unfractionated heparin, and often suggested higher patency and lower reocclusion rates at 5-7 day angiography after prolonged anticoagulation with the new agents.
These findings suggest that 'the ceiling' of pharmacological reperfusion may be reached, and underscore the need of a prolonged combined antithrombotic regimen of both anti-platelet and anticoagulant therapy to prevent recurrent thrombotic events in the first weeks to months after myocardial infarction.

Chapter 3 describes a randomized comparison of two antithrombotic treatment regimens for ST-elevation myocardial infarction: prehospital versus in-hospital fibrinolytic therapy. As part of the study protocol, with the prehospital care team screening the patient's eligibility, the in-hospital treatment times were markedly reduced, which resulted in a smaller difference in time to treatment between the two strategies than was anticipated, i.e. 32 minutes in stead of the often reported 50-60 minutes.
Although early outcome was not improved according to the randomized comparison, patients treated within 70 minutes after symptom had lower mortality and infarct size, and a higher global ejection fraction when compared to those treated later. These differences were not explained by differences in other characteristics but time to treatment. In the present long-term follow-up report, 2-year survival rates were 89% for prehospital and 91% for in-hospital fibrinolysis. The initial survival benefit for patients treated within 70 minutes was clinically sustained up to 2 years (98% vs. 89%) but was not statistically significant in the longer term. Event-free survival (clinical course free of death, reinfarction, revascularization, admission for angina, congestive heart failure) did not differ either. Moreover, time to treatment was not found to be an independent predictor of long-term outcome, neither as a continuous variable, nor as a dichotomous variable. Other factors such as age, a history of congestive heart failure or bypass surgery, or the need for coronary surgery after inclusion were independent predictors of long-term outcome.

These findings show that in the long-term many other factors determine outcome after fibrinolytic therapy. In addition to the clinical variables mentioned above, maintenance of a patent infarct-related artery after fibrinolysis could also be a likely predictor of outcome. This is addressed in **Chapter 4**, being the first report after fibrinolysis to address the long-term implications of reocclusion occurring in patients who survived the first 24-48 hours after reperfusion therapy and had an open infarct artery. A previous report, describing early reocclusion in patients after 90-minute angiography had demonstrated an increased risk of in-hospital mortality. In the APRICOT-trial no difference in 3-year survival was observed (> 90% in both groups), despite the fact that reocclusion, even in the absence of clinical reinfarction, was shown to have detrimental impact on the recovery of left ventricular function, the most important prognosticator after infarction. Patients in whom reocclusion was observed showed an increased risk for reinfarction (23% vs. 5% at one year)

and ischemia-driven revascularizations. The difference in outcome occurred in the first months after myocardial infarction and was sustained in the long-term when compared to patients without reocclusion in the 3 months after fibrinolysis.

Although quantitative overviews have suggested that therapy with aspirin reduces reocclusion of the infarct artery, little is known with respect to the potential impact on coronary artery disease progression in the non infarct artery, which is postulated to be a more subtle process, which involves phasic, often subclinical, non-occlusive thrombus formation. In **Chapter 5** a randomized placebo controlled 1-year angiographic follow-up study addressing the influence of anti-platelet therapy on coronary artery disease progression in the non infarct related arteries is presented in patients after ST-elevation myocardial infarction. At about one month after myocardial infarction, patients with an open infarct-related artery were randomized to either continue the combination of aspirin (50mg) and dipyridamole (400mg) or to matching placebo. A total of 1436 non infarct artery coronary segments were studied. The average change in QCA-parameters (MLD, diameter stenosis, mean luminal diameter) did not differ between groups. In a semi-quantitative analysis, the proportion of patients with progression was not affected by the combined anti-platelet regimen either (68% and 64%). Angiographic progression did not predict future clinical outcome. These findings underscore the previously suggested concept that anti-platelet therapy may not be effective in the often subclinical, subtle process of thrombusdeposition and organization of the plaque, as previously suggested in animal studies. It seems that the impact of anti-platelet therapy may be restricted to the prevention of acute events due to (sub)total occlusive thrombosis.

The randomized angiographic follow-up trial APRICOT-2 is presented in **Chapter 6**. The adverse clinical impact of reocclusion and its incidence of 25-30% in the first year after fibrinolysis calls for better preventive strategies, one of which is a more potent antithrombotic regimen. In 274 patients with TIMI-3 flow at inclusion angiography, performed within 48 hours after fibrinolysis, a prolonged, combined antithrombotic regimen of anti-platelet and anticoagulant therapy significantly reduced 3-month reocclusion, and improved recurrent ischemic events. Reocclusion was reduced from 28% to 15%. Reinfarction (8% vs. 2%) and ischemia-driven revascularizations (31% vs. 13%) were also significantly reduced on the combined regimen. The control antithrombotic regimen consisted

of 48 hours of intravenous heparin and the indefinite use of aspirin. The combined regimen consisted of the start of coumadin after the inclusion angiography, with heparinization until the target INR of 2-3. Consequently, heparinization lasted 66 hours longer in the patients allocated to coumadin (110 vs. 44 hours). Bleeding rates were higher on the prolonged combined antithrombotic regimen (5% vs. 3%), but no intracranial hemorrhages were observed. This conceptual study provided a mechanistic rationale to further investigate the role of prolonged anticoagulation after fibrinolytic therapy.

In **Chapter 7** the collective evidence of all randomized trials assessing the impact of the addition of oral anticoagulation to aspirin is reviewed. Given the prolonged hypercoagulable state after an acute coronary event, and the association of both a first and a recurrent acute coronary syndrome with the level of factor VII, the use of oral anticoagulation therapy seemed a promising intervention to further improve prognosis. Moreover, the fact that the risk reductions of oral anticoagulation therapy in placebo controlled trials was of the same magnitude as the reductions observed by aspirin underscored the potential of this regimen, especially now that lower doses of aspirin are used and the international normalized ratio (INR) has been introduced.

Importantly, regimens that merely focused on factor VII, and did not, or only slightly affected the INR, were not successful in improving outcome. A fixed, low-dose of vitamin K antagonists was used and monitoring was not necessary. CARS and LOWASA are examples of these trials. Although anticoagulant with respect to an effect on factor VII, these regimens did not have an antithrombotic effect: Bleeding increased, but thrombotic events were not reduced.

Other trials investigated the effect of dose-adjusted anticoagulant strategies that aimed to effect the generation of thrombin. With a reached INR > 2.0 dose-adjusted administration of vitamin K antagonists reduced recurrent thrombotic events, albeit at the expense of an increased risk of, primarily, minor bleeding. Intracranial hemorrhage rates were not increased. These findings in the clinical trials are in line with the observations in APRICOT-2. The Dutch ASPECT-2 trial and the Swedish WARIS-2 study are the most important clinical trials studying this regimen. Dose-adjusted anticoagulation with a reached INR < 2.0 did not result in better outcome either, as demonstrated in the CHAMP-trial.

Despite the evidence of a clinical benefit, the practical implementation of this

combined treatment strategy largely depends on a well organized infrastructure of INR monitoring. In view of the promising efficacy, the results of new anticoagulant agents such as the direct thrombin inhibitor ximelagatran with a more predictable effect, obviating the need for monitoring, are eagerly awaited.

Another strategy that has been prosposed in the prevention of reocclusion is a more aggressive approach with respect to revascularizations after fibrinolysis. In **Chapter 8** we studied the relationship between a severe residual stenosis after fibrinolysis and the chances for reocclusion and reinfarction, respectively. In APRICOT-1 a rather conservative, ischemia-guided revascularization strategy was followed, with only 11% revascularizations at 3 months. This offered the unique opportunity to study the 'natural course' of reocclusion and recurrent thrombotic events after fibrinolysis. Rationale behind the randomized studies on the impact of a routine invasive strategy was that routine angioplasty in patients with a severe residual stenosis would reduce reocclusion, and with it, reinfarction. Yet, an angiographic follow-up study performed in the same era questioned the relationship between a severe stenosis and reinfarction. In view of these observations we also studied this relationship in APRICOT-1.

With reocclusion being a predictor of reinfarction and recurrent events, the studypopulation was dichotomized according to the residual stenosis severity that best predicted reocclusion, i.e. a QCA-stenosis of 62.7%. Patients with a severe residual lesion (> 62.7%) had a reocclusion rate of 40% (47/118), as compared to 16% (20/122) for patients with a mild-moderate culprit stenosis. Notably, death and reinfarction rates did not differ between groups: 6% (7/118) vs. 9% (11/122). This is explained by the fact that in the case of reocclusion on a severe lesion this more often occurs without clinical reinfarction (15%; 7/47) when compared to reocclusion on a low-medium grade residual stenosis (55%; 11/20).

Whereas ROC-analysis was able to detect an optimal predictive residual stenosis for reocclusion, this was not the case for reinfarction. This suggests that periprocedural events rates may not have been the only explanation for the lack of benefit of the randomized trials on a routine invasive strategy. The fact that many of these angioplasty trials primarily focused on dilatation of severe lesions may also have contributed.

Our observations are in line with the only previous angiographic follow-up study showing an absence of association between stenosis severity and outcome after

successful thrombolysis, and extends these findings in the long-term. In the event of a future re-evaluation on the potential effect of a routine invasive strategy, these findings carry important implications for the design and protocol of such a study.

Chapter 9 is the first report on the impact of late reocclusion on long-term survival after fibrinolytic therapy in the setting of an ischemia-guided revascularization strategy. Whereas the prognostic consequences of early patency, reocclusion and reinfarction are undisputed, conflicting findings have been reported on the impact of late coronary patency.
Of the 248 patients of the APRICOT-1 trial 71 had reocclusion at 3-month follow-up angiography. Their 10-year cardiac survival rate was significantly lower when compared to 177 patients with sustained patency: 73% vs. 88%.
Interestingly, even in patients without ischemic symptoms until the time of the second angiography (no reinfarction,unstable angina or stable angina with positive stress testing) this difference was apparent: 73% vs. 85%. Thus, even in patients without recurrent ischemic symptoms, in whom reocclusion was merely detected as a result of systematic angiographic follow-up, reocclusion has adverse prognostic influence. The impact of reocclusion was independent of left ventricular function, which fuels the interest in the concept of late coronary patency.
This extension of our previously published 3-year follow-up project (Chapter 4), underscores the need to prevent late reocclusion, not only to reduce recurrent ischemic events, but also to improve cardiac survival. In contrast to previous new interventions the focus should be both on reinfarction and on clinically silent reocclusions. A combination of more potent antithrombotic regimens, with a more aggressive revascularization strategy at some timepoint after fibrinolysis seem to be the key elements for future studies to optimize outcome after pharmacological reperfusion therapy.

CHAPTER 12

Epicrise en Samenvatting

Epicrise

Dit manuscript heeft verschillende elementen van de antitrombotische behandeling van het acute ST-elevatie infarct bestreken. Daarnaast is geprobeerd inzicht te verschaffen in welke mate angiografische follow-up studies van belang kunnen zijn voor het verkrijgen van nieuwe inzichten omtrent de behandeling van het ST-elevatie infarct, zeker wanneer dit gecombineerd wordt met het vervolgen van de kliniek op de lange termijn.
Beschreven observaties, zoals het optreden van reocclusie in de afwezigheid van een klinisch reinfarct, en de mogelijke prognostische consequenties, benadrukken het belang van mechanistische studies geinitieerd door clinici zelf. Het lijkt tegenwoordig steeds meer gangbaar om snel grootschalige, veelal door de industrie georganiseerde studies te verrichten, vaak beperkt tot een vergelijking op klinische eindpunten op 4-5 weken na het infarct. Wellicht onder druk van de concurrentie, komt het zelfs voor dat angiografische voorstudies later worden gepubliceerd dan de daarop volgende klinische trials.
In tegenstelling tot de voornamelijk op klinische eindpunten gerichte studies, was het vooral een trial als de alom bekende GUSTO-1 studie die daadwerkelijk heeft bijgedragen aan ons inzicht in de behandeling, risicostratificatie en pathofysiologische concepten op het gebied van het ST-elevatie infarct. Deze studie had alle bovengenoemde elementen geincorporeerd in het protocol: naast een grootschalige vergelijking op klinische eindpunten, met daarbij lange termijn follow-up, werd ook een belangrijke angiografische substudie ingebouwd.
Bij de in dit proefschrift beschreven studies lag het initiatief bij de betrokken universiteit en clinici. De studievragen behelzen antitrombotische regimes waarvan de mogelijke consequenties voor de industrie in schril contrast staan met de hiervoor beschreven studies. Echter, zowel op het gebied van reperfusie therapie, als wat betreft de preventie van terugkerende trombotische events (intensievere antitrombotische therapie/aggressiever revascularisatiebeleid) leveren onze observaties aanvullende informatie voor toekomstig onderzoek en klinisch handelen.

Verbeteringen op het gebied van reperfusietherapie

Hoofdstukken 2 en 3. Met het bekend worden van de sterke associatie tussen TIMI-3 flow op 90 minuten na fibrinolyse en de overleving in de eerste maand na het

infarct, zijn er vele nieuwe middelen ontwikkeld die in een angiografische studie van bescheiden grootte werden uitgetest voordat een klinische studie werd verricht. Helaas is bij geen van de recentere grootschalige klinische reperfusie studies de moeite genomen een angiografische substudie in te plannen ter verificatie van de hypotheses gevormd op basis van angiografische pilotstudies. Hoewel verschillende middelen met angiografisch veelbelovende uitkomsten zijn getest, werd klinisch geen mortaliteitswinst waargenomen. Het gebrek aan systematisch verrichte angiografische, electrocardiografische en/of laboratorium substudies heeft er mede toe bijgedragen dat een diepgaande analyse naar een verklaring van het uitblijven van klinische winst met de nieuwe middelen niet mogelijk is.

Wellicht verblind in de zoektocht naar een nieuwer, potenter farmacologisch reperfusieregime, werden bepaalde basale richtlijnen in de praktijk niet optimaal gevolgd. Een nog immer belangrijk deel van de patiënten dat volgens de richtlijnen in aanmerking komt voor reperfusietherapie (fibrinolyse/primaire PCI) wordt niet als zodanig behandeld. Ook de vertragingen in het ziekenhuis voordat behandeling wordt geinitieerd worden vaak nog gebagatelliseerd, terwijl de potentiele impact van het reduceren van deze vertragingen vaak wordt onderschat. Analoog hieraan heeft het de nodige jaren gekost voordat prehospitale fibrinolyse programma's op grotere schaal werden geimplementeerd.

De MITI trial is één van de beste voorbeelden dat zelfs in de Verenigde Staten, met een straf en gecompliceerd juridisch stelsel, dit soort initiatieven met succes kunnen worden geimplementeerd. De te behalen winst is niet gering: uit kwantitatieve analyse van gerandomiseerde studies is gebleken dat per 1000 in de ambulance behandelde patiënten zo'n 16-18 levens kunnen worden gered in vergelijking met in het ziekenhuis geinitieerde fibrinolyse. De winst bereikt met prehospitale in plaats van in-hospitale initiatie van fibrinolyse is in dezelfde orde van grootte als bereikt met een primare PCI in plaats van in-hospitale fibrinolyse.

Directe vergelijkingen tussen prehospitale fibrinolyse en een primaire PTCA zijn schaars, en de enige gerandomiseerde studie tot dusver, helaas prematuur beeindigd, liet geen verschil in uitkomst zien. In deze studie werd een liberaal rescue beleid gevoerd na fibrinolyse. Deze bevindingen vereisen nader onderzoek, mede gezien de consequenties die de uitkomst van een dergelijke trial op de huidige logistieke problemen zou kunnen hebben ivm de toenemende vraag naar primaire PCI's. Aangezien de eindpunten reinfarct en reocclusie nu eenmaal frequenter zijn in geval van een relatief conservatief revascularisatiebeleid na farmacologische

reperfusie therapie, zullen toekomstige gerandomiseerde vergelijkingen met een primaire PCI een liberaal beleid wat betreft het verrichten van interventies na fibrinolyse moeten voorschrijven.
Nu ook voor de prognose na een primaire PCI is aangetoond dat de tijd tot behandeling van belang is, net als de flow in het infarctvat bij aanvang van de procedure, is het concept van de gefaciliteerde PCI geintroduceerd. Met het uur tijdswinst geboekt met prehospitale fibrinolyse, en het feit dat de 'door-to-balloon' tijd vaak nog 60-100 minuten bedraagt, zou de combinatie van prehospitale fibrinolyse met een daarop volgende interventie de optimale pact tussen farmacologische en mechanische reperfusie therapie kunnen betekenen. Verscheidende studies met varierende vormen van voorbehandeling (fibrinolyse, glycoproteine IIb/IIIa receptor blokkade of een combinatie van beide) zijn geinitieerd om dit concept te testen. Voortvloeiend uit bovenstaande ontwikkelingen, wordt in onze regio momenteel gewerkt aan een protocol gericht op patiënten met grote ST-elevatie infarcten (> 15 mm ST deviatie) die zich vroeg presenteren. Hierbij wordt gestreefd patiënten na toediening van aspirine en heparine prehospitaal te randomiseren naar ofwel 1. primare PCI danwel 2. fibrinolyse in de ambulance met daarna een interventie.

Noodzaak tot betere adjuvante antitrombotische therapie

Hoofdstukken 2, 4, 6, 7 en 9. Hoewel het vroegtijdig realiseren van goede antegrade coronaire flow van groot belang is, vormt het openhouden van het infarctvat een minstens even grote uitdaging: het optreden van een reinfarct en vroege reocclusie verdubbelen het risico op vroegtijdig overlijden. Tot dusver is de effectiviteit van antitrombotische regimes altijd uitgedrukt in de mate waarin het eindpunt dood/reinfarct gereduceerd werd. Met de vooruitgang geboekt in de behandeling van het infarct, is de frequentie hiervan dusdanig gereduceerd dat grote aantallen patiënten nodig zijn om significante verbeteringen aan te tonen. Wanneer ook reocclusie als eindpunt zou worden meegenomen, en als een scherper omschreven studiepopulatie zou worden bestudeerd, is het mogelijk met studies van beperktere omvang uit te komen.
Een methodologische vereiste voor onderzoek naar reocclusie is het verrichten van twee angiogrammen, waarbij randomisatie plaatsvindt nadat er TIMI-3 flow in het infarct vat is aangetoond. Met een incidentie van 7-10% ten tijde van ontslag, en van 20-30% in de eerste 3 maanden na het infarct, is het aantonen van een effect op reocclusie minder bewerkelijk dan op het eindpunt reinfarct dat in 4-5% van de

patiënten wordt gezien in de eerste maand na het infarct. Mede gezien de negatieve effecten op de kamerfunctie, zou ook dit als eindpunt gebruikt kunnen worden als indirecte maat voor overleving op de lange termijn. Via lange termijn klinische follow-up zou dit vervolgens kunnen worden gestaafd.
Indien follow-up angiografie op praktische bezwaren stuit, is het ook een mogelijkheid om vergelijkingen tussen antitrombotische strategieën te beperken tot patiënten bij wie het optreden van een klinisch reinfarct waarschijnlijker is. Hierbij valt te denken aan patiënten met electrocardiografische tekenen van reperfusie, en aangetoonde viabiliteit in het infarct gebied. In de huidige studies wordt veel van het potentiele effect van nieuwe middelen op terugkerende trombotische events verdund als gevolg van een behoorlijk aantal patiënten zonder reperfusie, of door een gebrek aan viabel myocard.
Deze manier van aanpak maakt studies van beperktere grootte mogelijk om een eerste indruk te krijgen van de potentiele effecten van nieuwe antitrombotische strategieën. In tegenstelling tot onderzoek bij vorige nieuwe medicijnen, zou meer aandacht kunnen worden besteed aan de kinetiek van deze middelen bij bepaalde patiëntengroepen, zeker omdat ze vaak kort na toediening van fibrinolyse worden toegediend. Hierbij zou gedacht kunnen worden aan ouderen en patiënten met een verminderde nierfunctie. Ook experimenteel dieronderzoek, een traject dat steeds minder uitgebreid wordt bewandeld, zou van toegevoegde waarde kunnen zijn in de verdere ontrafeling van het atherosclerotisch en trombotisch proces. Vervolgens zouden er grootschalige onderzoeken met angiografische en laboratorium substudies verricht kunnen worden met de middelen die in de meer conceptuele, mechanistische studies veelbelovend lijken.
Een ander belangrijk aspect met betrekking tot vergelijking van antitrombotische regimes betreft de duur van toediening en het eindpunt waarop de effectiviteit werd bepaald. Tot op heden is er geen overtuigend klinisch bewijs dat laag moleculaire heparines potenter zijn dan ongefractioneerde heparine. De veronderstelling dat deze middelen effectiever lijken wordt veroorzaakt door 2 factoren. Ten eerste is dit het gevolg van het feit dat de nieuwe middelen tot ontslag werden toegediend, in vergelijking met 48-72 uur ongefractioneerde heparine. Ten tweede werden reinfarcten die na ontslag optraden niet altijd meegeteld in het primaire eindpunt. Wanneer deze hierin wel betrokken worden, is er geen verschil in reinfarct waarneembaar.

Voor het ontwerp en de interpretatie van toekomstige studies kunnen dit soort factoren mee worden genomen. Bovendien zou door het verrichten van meer basaal laboratorium onderzoek in de grotere trials meer inzicht kunnen worden verkregen in het complexe proces van interactie tussen stollingsfactoren, plaatjesactiviteit en de associatie met terugkerende events.
Gezien de observaties uit APRICOT, waarin terugkerende trombotische events en reocclusie frequent voorkomen na successvolle fibrinolyse, zal één van onze toekomstige projecten gericht zijn op het fenomeen 'aspirine resistentie'. Ondanks een 20% relatieve risicoreductie sinds de invoering van aspirine na het infarct, kunnen vier van de vijf toekomstige events niet voorkomen worden. Het inschatten van welke (groep) patiënten hierop een verhoogde kans hebben kan nog worden verbeterd. De Study on Aspirin Resistance in major Antithrombotic (SARA) trials is ontworpen om dit proces pathofysiologisch nader te doorgronden en tot een gedegener definitie van dit fenomeen te komen op basis van klinisch, angiografisch en laboratorium onderzoek.

Routinematig versus een op ischemie gebaseerd interventiebeleid
Hoofdstuk 8. Hoewel voorgaande gerandomiseerde studies naar het effect van een routinematig invasief beleid geen winst ten opzichte van een 'ischemia-guided' strategie lieten zien, is een re-evaluatie noodzakelijk in het huidige tijdperk van verbeterde interventietechnieken. Periprocedurele events kunnen tegenwoordig worden gereduceerd met ongeveer 50% met gebruik glycoproteine IIb/IIIa receptor blokkade en bovendien is het materiaal verbeterd. Gezien de observaties uit 'ischemia-guided' studies met systematische angiografisch follow-up waarbij de kans op een reinfarct niet geassocieerd leek met de ernst van de reststenose, lijkt het simpelweg opnieuw uitvoeren van de gerandomiseerde studies van vroeger niet bijdragend genoeg. In deze studies werd het eindpunt gevormd door dood en reinfarct, terwijl dit na succesvolle fibrinolyse niet frequent voorkomt. Bovendien werden intermediaire leasies in de voorgaande onderzoeken vaak ongemoeid gelaten.
In analogie aan de studies naar het effect van nieuwe antitrombotische strategieën, lijkt ook hier het meenemen van een angiografisch eindpunt (doorgankelijkheid van het infarctvat op 6 maanden, reocclusie, kamerfunctie) een aanpassing die niet alleen tot een reductie van het benodigde aantal patiënten zal leiden, maar ook meer mechanistisch onderzoek mogelijk maakt.

Het onderzoek zal moeten uitwijzen of de verwachte voordelen van een routinematig revascularisatiebeleid zullen opwegen tegen de ook aanwezige procedurele risico's.
Onafhankelijk van de uitkomst van de studies, zal er inzicht worden verkregen welke patiënten(groepen) een grotere kans hebben op periprocedurele complicaties in het huidige tijdperk van verbeterde interventietechnieken. Mocht een routinematige invasieve strategie niet succesvol zijn, dan zouden deze data een meer op het individu toegespitste risicostratificatie mogelijk kunnen maken, die de basis zou kunnen vormen voor een electieve, risico-gestratificeerde, invasieve interventiestrategie.
Naar aanleiding van het bovengenoemde, is de gerandomiseerde APRICOT-3 studie ontworpen, waarin de waarde van een routinematige invasieve strategie zal worden onderzocht bij patiënten met een open infarctvat na fibrinolyse. Reocclusie en linkerventrikel functie zullen de primaire eindpunten zijn, en er zal lange termijn klinische follow-up plaatsvinden.

Van angiografie naar kliniek

Ondanks de bovenstaande voordelen en meerwaarde van het verrichten van angiografische (sub)studies is het belangrijk te realiseren dat dit specialistisch onderzoek betreft, niet alleen gezien de (geringe) kans op complicaties, maar vooral ook qua ontwerp en organisatie van de studie.
Ook het type studievraag bepaalt in hoeverre angiografie een geschikte methode is om een eerste indruk te krijgen van een bepaalde interventie. Zoals uit dit proefschrift blijkt, zijn studies naar (sub)totale afsluitingen in de coronairen na een ST-elevatie infarct goed te verrichten op voorwaarde dat een gedegen methodologie wordt gehanteerd. Echter, onderzoek naar minder uitgesproken veranderingen van de coronaire leasies is moelijker te interpreteren, deels vanwege de beperkingen die angiografie met zich meebrengt wat betreft de mogelijkheid tot detectie van de vaak geringe veranderingen.
Daarnaast spelen aspecten met betrekking tot de timing van het tweede angiogram een belangrijke rol: het niet op het moment van hernieuwde klachten, maar op een vast tijdstip verrichten van het follow-up angiogram doet waardevolle informatie verloren gaan bij patiënten die tussentijds opnieuw worden opgenomen voor een reinfarct of onstabiele angina. Slechts een aantal onderzoeksgroepen houdt rekening met deze klinisch geindiceerde, en daardoor vroeger dan geplande

follow-up angiografieën. Waarschijnlijk ondermeer hiermee samenhangend, is bij verscheidende therapieën die klinisch cardioprotectief bleken, maar zelfs ook bij middelen die in de kliniek protrombotisch bleken te zijn lieten, op angiografisch niveau geen duidelijke verandering waargenomen in het risico op coronaire trombose. Het is daarom van groot belang het type studiepopulatie, het soort medicatie en de te verwachten effecten mee te wegen in de afweging tot het al dan niet verrichten van angiografisch (follow-up) onderzoek.

Wanneer echter bovenstaande elementen goed worden overdacht, en het onderzoek door een ervaren groep wordt verricht, kunnen angiografische (sub)studies zeker bijdragen aan vergelijkingen van behandelingsstrategieën en het verfijnen van de risicostraficatie na het infarct om zo tot een meer op het individu toegespitste behandeling te komen.

Concluderend kan gesteld worden dat met de ontwikkeling van de 3 beschreven onderzoekslijnen er nieuwe mogelijkheden liggen om in de komende jaren middels de verkregen inzichten opnieuw vooruitgang te gaan boeken in de behandeling van patiënten na het acute infarct. Met het besef dat niet elke behandeling even succesvol is voor iedereen, en dat zowel qua effectiviteit en veiligheid verschillende risicoprofielen per patiënt bestaan, zal een verdere verfijning van een op het individu gerichte behandeling het streven moeten worden. Toekomstige onderzoeken zullen hier qua ontwerp en protocol op moeten inspringen, om zo een gedegen basis te leveren om deze vorm van klinisch handelen te ondersteunen en te perfectioneren.

Samenvatting

In de algemene introductie in **Hoofdstuk 1** wordt basale achtergrond informatie met betrekking tot acute coronaire syndromen beschreven en worden meer specifieke specialistische begrippen toegelicht die regelmatig in het manuscript terugkeren. In de uiteenzetting van het proefschrift worden beknopt de studievragen weergegeven, alsmede een korte beschrijving van de klinische en wetenschappelijke importantie.

Hoofdstuk 2 beschrijft de huidige standaard met betrekking tot de farmacologische behandeling van het ST-elevatie myocardinfarct. Daarnaast vormt het een kort historisch overzicht omtrent de ontwikkelingen op dit gebied en geeft het inzicht in de pathofysiologische rationale achter de productie en ontwikkeling van de nieuwe middelen.
Reperfusietherapie. Ondanks een sterke associatie tussen de TIMI flow in het infarctvat op 90 minuten na fibrinolyse en de kans op overlijden binnen 30 dagen, hebben nieuwe reperfusie regimes met hogere percentages TIMI-3 flow niet tot een reductie in mortaliteit geleid. Een voorbeeld betreft het gebruik van een halve dosis fibrinolyse gecombineerd met een glycoproteine IIb/IIIa receptor blokker. Bovendien was verwacht dat dit tot een reductie in het aantal bloedingen zou leiden, m.n. intracraniële bloedingen. Echter, bij patiënten boven de 57 jaar werd een verhoogd risico waargenomen, terwijl bij jongere patiënten minder hersenbloedingen voorkwamen op dit gecombineerde regime.
Adjuvante antitrombotica. Nieuw ontwikkelde producten op het gebied van antistolling leken superieur aan ongefractioneerde heparine wat betreft de preventie van reinfarcten en terugkerende ischemische events. In feite betrof het in de meerderheid van de gevallen een vergelijking van twee *strategieën* van antistolling, waarbij het nieuwe middel tot ontslag werd gecontinueerd terwijl de ongefractioneerde heparine voor 48-72 uur werd toegediend. Hoewel vaak het voordeel in reinfarcten tot ontslag wordt benadrukt, blijkt dat er na het stoppen van de nieuwe medicatie een “inhaalfenomeen” optreedt, zich uitend in vergelijkbare reinfarctpercentages op 30 dagen tot 1 jaar. Alleen de directe trombineremmer hirudine, in studies evenlang toegediend als ongefractioneerde heparine, lijkt daadwerkelijk een sterker antitrombotisch effect te sorteren, zich uitend in een lager reinfarctpercentage na fibrinolyse met streptokinase. Angiografische studies

met nieuwe antitrombotica rapporteerden vergelijkbare reperfusiepercentages op 90 minuten na fibrinolyse als ongefractioneerde heparine. Bovendien werd er een groter aantal open vaten en minder reocclusie bij angiografie voor ontslag beschreven na een strategie van langduriger antistolling met de nieuwe middelen. Deze bevindingen suggereren dat 'het plafond' van farmacologische reperfusie wellicht is bereikt, en ondersteunen het concept dat een langere periode van antistolling naast het gebruik van aspirine succesvol zou kunnen zijn in het verder reduceren van terugkerende trombotische events in de eerste weken tot maanden na een infarct.

In **Hoofdstuk 3** worden twee antitrombotische strategieën voor de behandeling van het ST-elevatie infarct gerandomiseerd vergeleken: prehospitale versus in-hospitale fibrinolyse. In het kader van het onderzoek inventariseerde het ambulance personeel al of de patiënt in aanmerking kwam voor reperfusietherapie, met als gevolg dat voor patiënten die gerandomiseerd werden naar behandeling in het ziekenhuis de tijdsduur tot initiatie van fibrinolyse sterk afnam. Deze afname van de vertraging in het ziekenhuis zorgde ervoor dat de tijdswinst ten opzichte van het starten in de ambulance minder uitgesproken was dan initieel verwacht: 32 minuten in plaats van de ongeveer 50-60 minuten in de meeste studies. Hoewel de prognose op korte termijn niet verschillend was in de gerandomiseerde vergelijking, hadden patiënten die binnen 70 minuten werden behandeld (ofwel pre- dan wel in-hospitaal) een lagere mortaliteit, een beperktere infarctgrootte, en een betere globale kamerfunctie in vergelijking met later behandelde patiënten. Deze verschillen werden niet verklaard door andere karakteristieken dan de tijd tot de start van behandeling. In de huidige lange termijn analyse, waren de overlevingspercentages op 2 jaar 89% voor prehospitale en 91% voor in het ziekenhuis gestarte fibrinolyse. Het initiele voordeel in overleving voor patiënten behandeld binnen 70 minuten bleef behouden tot op 2 jaar (98% vs. 89%), maar bleef niet significant hoger op de langere termijn. Event-vrije overleving (een klinisch beloop zonder overlijden, reinfarct, revascularisatie, heropname voor angina en hartfalen) was ook niet verschillend. Bovendien bleek de tijd tot behandeling geen onafhankelijke voorspeller van de uitkomst op lange termijn te zijn, noch als continue, noch als dichotome variabele. Andere factoren, zoals leeftijd, een voorgeschiedenis van hartfalen of bypass chirurgie, dan wel de noodzaak tot bypass chirurgie na inclusie bleken wel onafhankelijke voorspellers.

Deze bevindingen geven aan dat op de lange termijn vele andere factoren van belang zijn voor de prognose na fibrinolyse. Naast de bovengenoemde klinische variabelen, is het behouden van de doorgankelijkheid van het aan het infarct gerelateerde coronairvat mogelijk ook van prognostisch belang. **Hoofdstuk 4** is het eerste onderzoek na fibrinolyse dat de lange termijn gevolgen van reocclusie heeft beschreven in patiënten die de eerste 24-48 uur na reperfusietherapie overleefden, en een open infarctvat hadden. Een voorgaande publicatie, die het effect van vroege reocclusie bestudeerde bij patiënten met een angiografisch bewezen open infarctvat op 90 minuten na reperfusietherapie had een verhoogd risico op overlijden voor ontslag gerapporteerd.
In de APRICOT-studie werd geen verschil gevonden in de overleving op 3 jaar (>90% in beide groepen). Dit, ondanks het negatieve effect dat reocclusie heeft op de linkerkamerfunctie, zelfs wanneer dit optreedt in afwezigheid van een klinisch reinfarct. Patiënten bij wie reocclusie werd geobserveerd hadden een verhoogd risico op reinfarcten (23% vs. 5% op 1 jaar) en interventies, verricht ten gevolge van terugkerende ischemie in rust of bij inspanning. Het verschil in klinische uitkomst ten opzichte van patiënten bij wie geen reocclusie was opgetreden ontstond in de eerste maanden na het infarct en bleef over een periode van 3 jaar aanwezig.

Hoewel kwantitatieve overzichten het aannemelijk maken dat behandeling met aspirine de kans op reocclusie in de eerste twee weken na het infarct vermindert, is er weinig bekend over de mogelijke invloed op het meer sluipende proces van progressie van coronaire atherosclerose. Dit wordt verondersteld in fasen op te treden, meestal subklinisch, waarbij het met name om een meer subtiel proces van murale niet-occlusieve trombusvorming zou gaan. In **Hoofdstuk 5** wordt een gerandomiseerde, placebo-gecontroleerde studie met angiografische follow-up 1 jaar na een ST-elevatie infarct beschreven. Hierin wordt het effect bestudeerd van antiplaatjestherapie op het proces van atherosclerose in de kransslagaderen die niet tot het infarct hebben geleid. Dit werd mede onderzocht, omdat het starten van aspirine twee tot zes maanden na het infarct ook van prognostisch belang is gebleken, en de dan optredende events minder vaak aan het infarctvat gerelateerd zijn dan in de acute fase.
Op ongeveer een maand na fibrinolyse werden 154 patiënten met een open infarct arterie gerandomiseerd naar het continueren van antiplaatjestherapie (aspirine 50 mg en dipyridamol 400 mg) of placebo. In totaal werden 1436 coronaire

segmenten van de niet aan het infarct gerelateerde vaten bestudeerd op toename dan wel afname van de op het eerste angiogram waargenomen leasies, c.q. vernauwingen. De gemiddelde verandering in de middels kwantitatieve coronair angiografie geanalyseerde variabelen (diameter stenose, gemiddelde lumen diameter, minimale luminale diameter) verschilde niet tussen beide groepen. In een semi-kwantitatieve vergelijking, bleek de proportie patiënten met tekenen van angiografische progressie niet beinvloed (68% en 64%). Angiografische progressie was geen voorspeller van toekomstige klinische gebeurtenissen. Deze bevindingen ondersteunen de veronderstelling dat antiplaatjes- therapie geen effect sorteert op het vaak subklinische, subtiele proces van murale trombusdepositie en daarop volgende (re)organisatie van de plaque, zoals reeds eerder gesuggereerd via observaties in dierexperimenteel onderzoek. De werking van antiplaatjestherapie zou derhalve grotendeels berusten op de preventie van voornamelijk acute klinische events, veroorzaakt door (sub)totale occlusieve trombose.

De gerandomiseerde APRICOT-2 studie wordt gepresenteerd in **Hoofdstuk 6**. Gezien de negatieve gevolgen van reocclusie, en de incidentie van 25-30% in het eerste jaar na fibrinolyse, is betere preventie vereist. Dit zou ondermeer bereikt kunnen worden middels meer intensieve antitrombotische regimes. Bij 274 patiënten met TIMI-3 flow in het infarctvat tijdens de inclusieangiografie, verricht binnen 48 uur na fibrinolyse, bleek een gecombineerd antitrombotisch regime van antiplaatjestherapie met antistollingstherapie gecontinueerd voor 3 maanden de incidentie van reocclusie op 3 maanden significant te verminderen: 28% vs. 15%. Het aantal reinfarcten (8% vs. 2%) en op basis van ischemie verrichte revascularisaties (31% vs. 13%) was ook significant lager op het gecombineerde antitrombotische regime. De controlearm werd behandeld met de gebruikelijke 48 uur intraveneuze heparine en het gebruik van aspirine voor onbepaalde tijd. Het te testen antitrombotische beleid bestond uit het starten met coumarinederivaten nadat bij inclusieangiografie een open infarctvat was aangetoond, terwijl de heparine werd gecontinueerd totdat de streefwaarde van de INR was bereikt (2-3). Als gevolg hiervan was de totale duur van hepariniseren 66 uur langer in de patiënten gerandomiseerd naar het gebruik van coumarine (110 vs. 44 uur). Het bloedingsrisico op het nieuwe regime verdubbelde, maar bleef acceptabel: intracraniele bloedingen werden niet waargenomen. Deze conceptuele studie geeft een mechanistische verklaring voor het potentiele effect van de toevoeging

van langdurige antistollingstherapie aan aspirine, en vereist confirmatie in grote klinische studies.

Hoofdstuk 7 betreft een review van alle gerandomiseerde studies naar het effect van het toevoegen van orale antistolling aan aspirine na een acuut coronair syndroom. Met het bestaan van een verhoogde stollingsactiviteit tot op 6 maanden na een acuut coronair syndroom, en de associatie tussen factor VII en zowel een eerste infarct als een recidief infarct, lijkt het gebruik van orale antistollingstherapie een veelbelovende interventie om de prognose gunstig te beinvloeden. Zeker nu er heden ten dage lagere doseringen aspirine worden voorgeschreven, en het effect van antistollingstherapie beter kan worden gecontroleerd na de introductie van de INR is de hernieuwde interesse voor deze behandelingsoptie te begrijpen.
De onderzoeken verschilden qua pathofysiologische rationale en dientengevolge in de intensiteit van antistolling. Een deel van de studies was erop gericht de concentratie van factor VII te beinvloeden met een lage gefixeerde dosis orale antistolling, zonder wezenlijk effect op de INR. Voorbeelden zijn studies als CARS en LOWASA: ondanks additie van een anticoagulans met effect op factor VII, en een verhoogd bloedingsrisico, bleek er geen antitrombotisch effect in de zin van een verminderde kans op terugkerende trombotische events.
In andere onderzoeken werd via hogere doseringen orale antistollingstherapie, getitreerd middels herhaaldelijke INR controle, ook een effect op trombine nagestreefd, zich vertalend in een duidelijke verlenging van de INR. Wanneer een INR > 2.0 werd bereikt, zoals in de WARIS-2 en ASPECT-2 studies, werd wel een verbetering in klinische uitkomsten waargenomen, voornamelijk bepaald door een reductie in terugkerende trombotische events, met een verhoogd risico op bloeden als keerzijde. De kans op intracraniele bloedingen werd echter niet verhoogd. De observaties in deze klinische studies liggen in lijn met die van de angiografische APRICOT-2 studie. In het geval dat een INR < 2.0 werd bereikt, zoals in de CHAMP-studie, bleef het gewenste klinische effect uit.
Ondanks een bewezen klinisch effect, heeft het gebruik van vitamine K antagonisten geen algemene ingang gevonden, wat deels samenhangt met het feit dat het succes afhankelijk is van een goede infrastructuur wat betreft INR controle. Gezien het bewezen effect van langdurige, intensieve orale antistollingstherapie, waarbij ook trombine wordt beinvloed, worden de resultaten van nieuwe middelen als de directe trombineremmer ximelagatran met spanning afgewacht, omdat regelmatige monitoring dan niet noodzakelijk is.

Een andere strategie die geopperd is om reocclusie succesvoller te voorkomen is een aggressiever revascularisatiebeleid na fibrinolyse. In **Hoofdstuk 8** bestudeerden wij de relatie tussen een ernstige reststenose na fibrinolyse en de kans op het optreden van reocclusie enerzijds, en de kans op een reinfarct anderzijds. In de APRICOT-1 studie werd een redelijk conservatief interventiebeleid gevoerd, op geleide van ischemie, met slechts 11% revascularisaties op 3 maanden. Dit maakte het mogelijk het "natuurlijke proces" van reocclusie en terugkerende trombotische events na fibrinolyse te bestuderen. De rationale achter de gerandomiseerde studies die het effect van een routinematig revascularisatiebeleid onderzochten was de volgende: door systematisch patiënten met een ernstige stenose te dotteren, onafhankelijk van klachten, zou het risico op reocclusie afnemen, en daarmee de kans op een reinfarct. Een angiografische follow-up studie uit dezelfde periode deed echter vermoeden dat de kans op een reinfarct niet samenhangt met de ernst van de reststenose na fibrinolyse.

Vandaar dat in APRICOT-1 deze relatie eveneens is onderzocht. Aangezien reocclusie een belangrijke voorspeller is van reinfarcten en terugkerende ischemische events, werd de studiepopulatie verdeeld op basis van de reststenose die de kans op reocclusie optimaal voorspelde: een stenose van 62.7% bepaald middels kwantitatieve coronairangiografische analyse. Patiënten met een ernstige reststenose hadden een kans van 40% (47/118) op reocclusie, vergeleken met 16% (20/122) bij patiënten met een minder ernstige reststenose. Opvallend was dat de reinfarctpercentages niet significant verschilden tussen de beide groepen: 6% (7/118) vs. 9% (11/122).

Dit wordt verklaard door het feit dat in geval van reocclusie op een reeds ernstige restleasie een klinisch reinfarct minder vaak optrad (15%; 7/47) dan bij reocclusie op een minder uitgesproken vernauwing (55%; 11/20).

Hoewel middels ROC-analyse wel een optimaal predictieve reststenose voor reocclusie kon worden gevonden, was dit voor het reinfarct niet het geval. Met andere woorden: op basis van de ernst van de reststenose viel het optreden van een reinfarct na succesvolle trombolyse niet te voorspellen. Dit suggereert dat het verhoogde aantal periprocedurele events wellicht niet de enige verklaring vormt voor het ontbreken van een klinisch voordeel van een routinematige revasculari satiestrategie. Deze observaties, gekoppeld aan het feit dat in voorgaande studies vaak alleen de ernstiger leasies werden gedotterd, kunnen van belang zijn voor het ontwerp van een toekomstige herevaluatie van deze strategie. In de loop der jaren

zijn de interventietechnieken immers sterk verbeterd, worden periprocedureel glycoproteineblokkers gebruikt, en is het bovendien gebruikelijker geworden ook minder ernstige leasies te dotteren.

Hoofdstuk 9 is de eerste beschrijvende studie waaruit blijkt dat ook bij patiënten die de eerste 24-48 uur na fibrinolyse voor een infarct overleven, en behandeld werden volgens een "ischemia-guided" revascularisatie strategie, het optreden van reocclusie in de maanden daarna van prognostische betekenis is.
Van de 248 patiënten in de APRICOT-1 studie werd bij 71 patiënten reocclusie geconstateerd (29%). De cardiale 10-jaars overleving was significant slechter in het geval van reocclusie: 73% vs. 88%. Zelfs bij patiënten zonder aperte tekenen van terugkerende ischemie tot follow-up angiografie (reinfarct, onstabiele angina, stabiele angina met positieve stress test) was dit effect aanwezig: 73% vs. 85%.
Kortom, zelfs bij patiënten zonder klinisch geobjectiveerde terugkerende ischemische klachten, bij wie reocclusie puur als gevolg van systematische angiografie werd ontdekt, lijkt reocclusie een negatief effect op de prognose te sorteren. De prognostische consequenties bleken onafhankelijk van linkerventrikelfunctie, de enige andere onafhankelijke voorspeller van 10-jaars overleving.
Deze extensie van ons eerder gepubliceerde 3-jaar follow-up project (hoofdstuk 4), benadrukt de noodzaak tot verder onderzoek naar preventieve strategieën, ook gericht op na ontslag optredende reocclusies. Niet alleen in de hoop het aantal ischemische events te reduceren, maar ook om wellicht de cardiale overleving te verbeteren. In tegenstelling tot voorgaande preventieve strategieën, zal de focus niet alleen op reinfarcten gericht moeten zijn, maar ook op stille reocclusies. Een combinatie van krachtiger antitrombotische regimes en een aggressiever revascularisatiebeleid na fibrinolyse vormen de belangrijkste elementen voor toekomstige studies ter optimalisatie van de prognose na fibrinolyse.

PART 4 Addenum

Dankwoord

De weg naar een proefschrift is lang, en op die weg kom je vele mensen tegen die allemaal, ieder op zijn/haar eigen manier, hebben bijgedragen aan de totstandkoming ervan. In het geval van multicentrum studies is de lijst met mensen aan wie ik dank verschuldigd ben uitgebreid, helemaal wanneer één van die studies in het buitenland heeft gelopen zoals het geval was bij de MITI studie uit Seattle, USA. Vandaar dat ik mij tot de meerderheid zou willen richten met algemene dankzeggingen, om vervolgens een aantal mensen in het bijzonder te bedanken.

Hoewel vaak als vanzelfsprekend beschouwd, begint de mogelijkheid tot onderzoek met instemmende patienten, in dit geval meer dan 600 die bereid waren twee coronair angiografie onderzoeken te ondergaan. Daarnaast is in verschillende ziekenhuizen moeite gedaan om een speciale infrastructuur te ontwikkelen om angiografisch follow-up onderzoek tot een succes te maken. Alle betrokken artsen, arts-assistenten, verpleegkundigen en secretaresses van de betreffende centra verdienen hiervoor een groot compliment.

Wat betreft de spilfiguren op het gebied van studie en werk zijn Professor Verheugt, Dr. Weaver en Jan Böhncke de grondleggers van de in mij ontstane 'drang' tot het onderzoeksbestaan.

De spilfiguren

Prof. Dr. F.W.A. Verheugt, beste Freek:
Grenzeloos enthousiasme en een bewonderenswaardige punctualiteit wat betreft afspraken zijn twee zaken die mij altijd zullen bijblijven als ik terugdenk aan de meer dan dertien jaar samen onderzoek doen. De grote vrijheid en verantwoordelijkheid die ik van u kreeg, niet alleen voor mijn eigen werk, maar ook om 'in de kelder' een onderzoekstoko op te zetten, waardeer ik enorm. Een dergelijke samenwerking op basis van wederzijds vertrouwen, waarin openheid centraal staat, maak je maar zelden mee. Ik hoop dat we daar nog lang de vruchten van mogen plukken!

Dr. W. D. Weaver, dear Doug:
My experience as a research student at the MITI office in 1994 undoubtedly fuelled my interest in future projects. I specifically remember the combination of a very

professional, efficiently organized center and a nice, lively atmosphere. Your sense of humour will certainly have contributed to it. Unlike many doctors in the field of research, you also emphasized to take enough time to personally study the acquired data thoroughly (linear, curvilinear, U-shaped relationship), and stimulated me to gain more in-depth knowledge with regard to statistical analyses.

Drs. J. Böhncke, beste Jan:
Zonder jouw assertieve houding had ik nooit aan zo'n vruchtbare wetenschappelijke stage gekomen als de lange termijn follow-up van APRICOT! Zeker wat betreft het leren organiseren van zaken, net binnen of net buiten de regels om, en het krijgen van inzicht in politieke spelletjes heb ik als 19-jarig mannetje veel van je meegekregen. En bovenal, dat als je ECHT iets wil, je er (bijna) altijd komt…Grote bewondering voor wat je allemaal zelf hebt klaargespeeld!

Bovengenoemden vormden de basis voor een prachtige onderzoeksperiode, maar zonder opslag en verwerking van data zou er weinig van terecht zijn gekomen. In dat kader wil ik met name Johan Karreman, Gérard Uijen en Truus Peijnenburg bedanken.

De data-managers

VUmc, Amsterdam:
Beste Johan, het duurde even voordat ik doorhad hoe het moest, dat communiceren in databasecodes, maar inmiddels hebben we elkaars taal toch zeer goed leren spreken!

UMC Nijmegen:
Allereerst natuurlijk onze 'nestor'. Beste Gérard, ik heb minstens net zo veel geleerd van je verhalen over de geschiedenis van de cardiologie in het Radboud, en niet te vergeten "Het Bureau" van Voskuil, als van je gedegen statistiek onderwijs. Verder was je op belangrijke momenten een waar vaderfiguur, waarvoor dank.
Voor Truus een aparte passage…los van je werk aan de APRICOT-database en je moed om te doen wat goed was voor het slagen van het project… We hebben veel meegemaakt, en ik heb je leren kennen als iemand die erop 'gebrand' is

'volle bak' te geven, en kwaliteit na te streven. Weinig mensen weten hoezeer de onderbezetting tot 2001 zijn tol heeft geeist met Gérard, jij en ik als kampioenhouders vakantiedagen. Ik hoop van harte dat je er binnenkort weer vol vuur en vlam tegen aan kunt gaan, máár…wel met een beetje meer de handrem erop!
Resten nog Rudi, Noor en Gabe. Weliswaar niet direct betrokken bij het project, maar toch. De laatste twee hebben er voor gezorgd dat er weer ademruimte is op de experimentele, wat zich direct heeft vertaald in een meer ontspannen sfeer, van groot belang om optimaal te kunnen functioneren. Rudi zal ik onthouden in een dubbelrol, eerst als promovendus en nu als vervanger van Gérard. Dubbelrol is eigenlijk een understatement, je lijkt wel een octopus, met een ongekend improvisatievermogen. Heel veel succes, en dat je na een hectische start de ingeslagen weg tot een gestructureerde, stabiele ondersteuningsafdeling maar mag perfectioneren!

Naast technische ondersteuning is ook controle van het werk en de data van groot belang. Hierbij hebben mijn co-promotoren een belangrijke rol gespeeld, zeker gezien het feit dat er meer dan 300 paar 'films' moest worden beoordeeld.

De co-promotoren

Dr. G. Veen, beste Gerrit:
Initieel als auteur in jouw proefschrift contact gekregen, en inmiddels als mijn begeleider een vaste rots in de branding. Vooral je systematische aanpak van zaken, of het nu een film, een casus of een artikel is, heeft ook mijn eigen manier van handelen positief beinvloed. Daarnaast was het altijd fijn om een nuchtere blik van 'buiten' te hebben, op momenten dat men in Nijmegen te kort door de bocht dreigde te gaan.

Dr. W.R.M. Aengevaeren, beste Wim:
Prachtig om te zien hoe iemand van zijn vak kan genieten, hoe vol je kon zijn van een prachtige film! Je enorm hoge tempo, je discipline, toewijding en perfectionisme zijn een voorbeeld voor een ieder. Ik ervaar het als een groot compliment dat ik je presentaties mag controleren, en het protocol voor interventiecardiologie heb mogen screenen. Leuk om zoveel angiografische kennis van je te hebben meegekregen! En nu op naar APRICOT-3!

Zeker omdat de APRICOT-studies voor een groot deel draaien om de organisatie in en rond het cathlab wil ik het personeel aldaar nogmaals extra bedanken voor hun medewerking en de daardoor onstane band, ook voor het verrichten van nieuwe studies. In het bijzonder wil ik dit keer iemand bedanken die het strijdtoneel gaat verlaten: Ingrid Steinmann. Zowel op het persoonlijke vlak als op het werk was het een waar genot je te hebben leren kennen: een representatieve, goede secretaresse als jij is met recht een visitekaartje, en van groot belang voor de eerste indruk die men krijgt over een afdeling. In het Canisius Wilhelmina Ziekenhuis verdienen Astrid Schut en Tineke Tiemes een speciale vermelding voor hun soepele, goede en gezellige samenwerking. Uit mijn studententijd wil ik graag twee secretaresses bedanken: één uit Nederland en één uit Amerika. Allereerst Tineke Welle, die ik me vooral herinner om haar enorme gevoel voor humor. From Seattle, Washington, USA, Miss Mona J Ries should be mentioned for her hospitality and the training she gave me to learn how to type faster than lightning. Thank you so much!

Resten nog de 'jongens uit de kelder', een begrip geintroduceerd door Janneke Timmermans.

De jongens uit de kelder

Ralf 'Overmars' Vromans, beste Ralf:
Redenen te over om jou te bedanken. Als één van de grondleggers van de nieuwe aanpak en sfeer rondom het APRICOT-project verdien jij alle credit: tot in Groningen toe (lift Mercure, TCC) heb je jezelf onsterfelijk gemaakt! Je baan opgegeven om als student er volop met mij tegenaan te gaan. Onze haast maniakale manier van samenwerken kon maar op één voorwaarde goed gaan: de ultieme klik! En die was er… Altijd vonden we wel weer een manier om 'must' met 'lust' te combineren! Eén en al prachtige herinneringen en verhalen…En eh…dat week-endje Papendal, dat heb je nog te goed! Ralf, je bent uit mijn leven niet meer weg te denken. For better and for worse…dat weet je..

Peter 'Middle Initial' Kievit, beste Peter:
Zonder jouw hulp was het nooit gelukt om na APRICOT-2 de doorstart op de experimentele te realiseren. Toegegeven, het kostte wat bekeerwerk, maar

uiteindelijk bracht jij onder woorden wat ik je bedoelde te zeggen: het draait om onafhankelijkheid van geest. Hoezo te oud voor onderzoek? *Dacht het niet!!* Persoonlijke ontwikkeling, in plaats van snel mijlpalen op CV's scoren. Een verhelderende nachtje in Curaçao gaf de doorslag….. En zo werden we een bevlogen, keihard werkend, superkritisch, en bij vlagen flamboyant duo (briefje Astra, podium New Orleans). Statler en Waldorf! Dank voor al je hulp en de mooie momenten. Nog meer dan de werkrelatie, koester ik de herinneringen aan de uren die we daarbuiten doorbrengen. Weten dat het goed zit. Voor elkaar door het vuur. Er zijn… Elkaar kennen van A tot Z: blindelings aanvoelen en aanvullen. Mooi…

Jaap 'De Bison' Remmen, beste Jaap:
Een visitekaartje voor ons vak, dat ben je! Je liefde voor mensen, je goede hart, je drive om te knallen, en juist ook je sigaretten…Heeerrrrrrrrrrrrrrrrrlijk! En vooral ook onze telepathische momenten, prachtig! De enthousiaste telefoongesprekken als je weer een mooie bevinding had gedaan, je ondeugende analytische vermogens (van wie zou je die nou hebben?), en de gezellige avondjes doorhalen in de kroeg of op de experimentele (ja…op de experimentele!). Een gouden gooser ben je, seeker weten! Samen met Peter altijd de meest kritische lezer van mijn stukken, waarvoor dank. Grote bewondering hoe je er vol in bent gegaan, promotie én opleiding, als echtgenoot en vader van twee kinderen. Japie, nog even volhouden, mijn steun heb je!

Etienne 'The Philospher' Cramer, beste Etienne:
Troponine Billy, The Artist, The Genius het had allemaal gekund…Maar eigenlijk ook juist weer niet, natuurlijk….De man van de vele opties en de vele invalshoeken.. Etienne, het is me een waar genoegen dat onze paden zijn gekruist! Blind vertrouwen vanaf dag één, het allergrootste goed… Mooie, diepe gesprekken, openheid, en wederzijds begrip. Vriendschap met een hoofdletter V. Turijn, Milaan, Riccione, Florence…..Marathonacties…door kunnen zetten, af kunnen maken…
Na het vertrek van Peter was jij het die mij scherp hield, zowel met je immer doordachte op- en aanmerkingen op mijn artikelen, APRICOT-3 en SARA, als met je eigen, vaak originele onderzoeksvoorstellen. Mijn 'van Persie'! En dat voor een Ajax-fan! Leuk dat ik je heb mogen enthousiasmeren…ontluikende bevlogenheid! Cramertje, it's all mental, dus jij haalt zeker ook jouw doel!

Hendrik-Jan 'Excuus' Dieker, beste Hendrik-Jan:
Siamo nati bucati per non morire crepati! Als één van de weinigen van 'the young generation' nog écht beseffend dat keihard werken één van de voorwaarden van succes is… HIS ging dan mis, maar Nieuw Zeeland was toch een mooi alternatief! Hoop wel dat je bij toekomstig onderzoek minder last zult hebben van grillen van bazen en een beter georganiseerde financiële- en infrastructuur zult treffen. Grote klasse hoor, met welke toewijding jij jezelf probeert te 'trainen', en vooral dingen die je moeilijk of lastig vindt niet uit de weg gaat! Op weg om de 'Encyclope-Dieker' van het ST-elevatie infarct te worden! Maar amico, vergeet niet hoe belangrijk de 'cooling down' is (minstens net zo belangrijk als stretchen?!), ook voor de 'tensione': Een avondje relaxen met een lekkere Merlot, of wordt het toch een Rosso di Montalcino???

Nick 'Interesting' Clappers, beste Nick:
Menigeen zal denken dat jij als waar neerlandicus al wat fouten in mijn Nederlands hebt ontdekt, maar gelukkig weet ik dat jij andere dingen 'far more interesting' vindt. Als je je daar niet te veel door laat afleiden, en er wellicht zelfs een beetje 'resistent' voor wordt (tijdelijk dan), dan weet ik zeker dat het met SARA en jou wel goed komt. Erg leuk om samen al zo veel gedaan te hebben, zowel qua 'stukken' (schrijfwerk wel te verstaan) als de uitjes Amerika en Italië. Vergeet nooit hoe je ooit student Nick 'met het vingertje' was: dat is de Nick voor wie ik me hard heb gemaakt op de experimentele. Nicky Nick, jongen, zorg dat opa trots op je zou zijn!

Wessel 'The Resuscitation Kid' Keuper, beste Wessel:
Na heel veel geduld eindelijk je verdiende plek gekregen: en zo hebben we nu drie oud wetenschappelijke stage lopers als opvolgers. Knap hoe je hebt volgehouden, één van de belangrijkste eigenschappen om een promotie af te ronden, overigens. Als student bleek al dat je er een hoop naast kunt doen (Hippocrates) en hebben: privé was je voor je familie een rots in de branding. Voor zo'n jong menneke als jij, al een volwassen instelling. Uit het goede hout gesneden! Zorg wel dat er gevoetbald blijft worden, hè! En laat Gomes en Camaro dan ook maar eens rennen! Tips voor een avondje relaxen, zoals genieten van een lekker muziekje of bijvoorbeeld lekker uit eten met een goed glas wijn, tja…die hoef ik jou niet te geven!

Part-time 'experimentelen' die zeker niet vergeten mogen worden zijn Paul van den Bergh en Aline Huizenga. Aline, denk terug aan mijn speech tijdens je feest en je weet wat ik je wil zeggen. Paul, onvoorstelbaar wat jij aan werk weet te verzetten. Veel geleerd van je 'verleg-het-initiatief' strategie, risico stratificatie en financiële trucs. Wat betreft het onderzoek: degene met de langste adem komt er altijd, dus blijf ademenen, ha,ha!
Hoewel het dus voornamelijk jongens in de kelder zijn, moeten ook Suzanne Jacobs en Irene Joziasse vermeld worden, dames die altijd voor een extra tintje qua sfeer wisten te zorgen. Suzanne, dank voor je luisterend oor, de gezellige momenten met wat druiven, kaas en wijn op de flat, je heerlijke improvisatievermogen en onvoorwaardelijke vriendschap. Verder wil ik Joke de Lange expliciet bedanken voor alle mooie werk- en privémomenten, en natuurlijk de goede en vooral ook altijd gezellige samenwerking. Tot slot, Diana Wuijster, hartstikke bedankt voor het altijd attente meeleven, en de vaak perfecte hulpacties bij surpriseparties, mijn ceremoniemeesteractiviteiten en speuracties naar Boss broeken. Blijven gáán hè!?!

De allerbelangrijksten

Zonder twijfel zijn dat mijn ouders… Mede dankzij de door hun meegegeven levensinstelling, en de geboden kansen en vrijheid, heb ik me kunnen ontwikkelen tot wie ik nu ben. Lieve mam, grote bewondering voor je hoe 'het leven na pappa' hebt opgepikt, dank voor je onvoorwaardelijke steun, en je hulp in de week-enden als ik weer eens ouderwets verwend werd en niet hoefde te koken. Daarnaast natuurlijk mijn zussen, die in allerlei privésituaties te hulp zijn geschoten. Naast Maarten en Jeroen, verdient vooral Wim een extra bedankje: wat rijdt mijn auto toch heerlijk!!

In de roes richting de finish hoop ik dat ik niemand vergeten ben…

Onderzoek doe je met zijn allen, en ik hoop van harte dat die sfeer zich alleen nog maar sterker zal doorvertalen binnen onze afdeling. Dank aan allen die hier tot nu toe aan hebben bijgedragen!

Bloemlezing

Hartelijk dank voor uw medewerking !

Met vriendelijke groet,

De APRICOT-1 onderzoekers

PK LOOPT NL 10x de AVOND
VIERDAAGS IN WINSCHOTEN
10 km AVOND
OOK BENJH LID VAN EEN CODEBOEL CLUB
EN DART VERENIGEN (WIJ BEGINNEN
MET 301 TEGOOIEN)
TEN SLOTTEN HEB IK NOG EEN
VRIENDIN (OUD 76 JAAR) IK BEN 71 JAAR

N.B. IK HEB NIEMAND AAN DE APRICOT-1 STUDIE NA HET HARTINFARKT MEEGEDAAN. HAAR IK BEN TOEN NA ± 5 DAGEN GESTOPT MET MEDICATIE OMDAT IK TOEN VANAF HET MIDDEN VAN MIJN BEENTJE AAN MIJN TENEN ALLERLEI RODE PLEKKEN DIE ENORME JEUK VEROORZAAKTEN KREEG.
HOPENDE DE U VOLDOEN DE TE HEBBEN INGELICHT VERBLIJF IK MET VRIENDELIJKE GROETEN.

Van: Fam vd Bergh RE fupbrieven
Verzonden: donderdag 5 december 2002 17:33 bergh@chello.nl]
Aan: Kievit P.
Onderwerp: RE: fupbrieven

Geachte heer Kievit,

Uw fubbrieven hebben mij in goede staat bereikt.
Alleen ben ik niet de van den Bergh aan wie u ze wilde sturen.
Ik ben juist degene die zorgt dat u patienten krijgt, ik heb namelijk een cafetaria.
Dus kijkt u even het mail-adres van uw collega na.

groeten

Pam van den Bergh

-----Oorspronkelijk bericht-----
Van: Kievit P. [mailto:P.Kievit@cardio.umcn.nl]
Verzonden: donderdag 5 december 2002 10:28
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<<ConceptAlfollowupvragenlijst.doc>> <<ConceptBrief10-yearFUP.doc>>

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Curriculum Vitae

De 'brouwer' van dit proefschrift werd geboren op 24 maart 1971 te Bussum. Een van jongs af aan aanwezige, spelenderwijs ontstane interesse in 'het waarom' zou wel eens de voedingsbodem kunnen hebben gevormd voor een niet aflatend enthousiasme voor onderzoek, wellicht in lijn met de door Einstein gebezigde woorden: "Play is the highest form of research". Hoewel door sommigen omschreven als 'homo ludens' (spelende mens), heeft het opnieuw moeten leren lezen en rekenen na een hardnekkige meningitis zeker ook bijgedragen aan de tevens bij onderzoek vereiste serieuze houding en het ontwikkelen van een systematische methodiek van werken en onthouden.

In 1989 werd gestart met de opleiding geneeskunde aan de Vrije Universiteit in Amsterdam. Samen met Jan Böhncke begon reeds in 1991 een periode van wetenschappelijk onderzoek, op de afdeling cardiologie, onder begeleiding van Prof. Dr. F.W.A. Verheugt: een project dat resulteerde in een beloning van de Hartstichting, met de mogelijkheid tot nieuw onderzoek in Seattle, USA. Dit gebeurde onder leiding van een onderzoeker pur sang, Dr. W. Douglas Weaver, organisatorisch brein achter het superprofessioneel gerunde onderzoeksinstituut van o.a. de MITI studie.

Na het cum laude afsluiten van de doctoraalfase in 1994, werd het doen van co-schappen initieel ervaren als een bijkomstigheid, samenhangend met het plotseling overlijden van één van zijn grote voorbeelden, vader Martin Brouwer. Niet in de laatste plaats zal deze periode hebben bijgedragen tot een onomstotelijk geloof in het eigen improvisatievermogen, maar vooral ook tot het geloof in het 'on(be)grijpbare hogere', het wetenschappelijk onverklaarbare.

Tijdens het keuze co-schap cardiologie, werd door Prof. Verheugt, inmiddels hoogleraar te Nijmegen, de opleiding in het verschiet gesteld op twee voorwaarden: promoveren en de eerste aanzet geven tot het opzetten van een onderzoeksafdeling. Na het cum laude behalen van de artsentitel in 1997, werd met de in het westen opgedane ervaring afgereisd om op onderzoek uit te gaan in het oosten.

Initieel beschouwd als de wat vreemde eend in de bijt, de eerste assistent full-time vrijgepland voor onderzoek, is geleidelijk een cultuur ontstaan waarin het onderzoek groeide en bloeide. In 2000 werden alle inspanningen, afdelingsbreed, bekroond met een uitnodiging tot een Hotline-presentatie over de APRICOT-2 studie en wel op het hoogste internationale platform in Europa, tijdens het Europese cardiologie congres in de RAI te Amsterdam. Daarna volgde een periode waarin het met name het enthousiasmeren en begeleiden van andere assistenten

centraal stond, evenals het opzetten van een internationale samenwerking met een gerenommeerde onderzoeksgroep uit Nieuw Zeeland. Na lang volhouden kwam er ook geld voor vervolgonderzoek, zowel via de industrie (Eli-Lilly, 2000) als via de Hartstichting, middels twee gehonoreerde subsidieaanvragen (2004).

Daar waar door velen promoveren als 'goede hit' op het CV wordt beschouwd, met een boekje als einddoel, kan het voor sommigen een "way of life" worden, iets waaraan je verknocht raakt, waarin je anderen wilt meekrijgen, een periode van persoonlijke ontwikkeling op vele terreinen…Na vele jaren 'onderzoek op gebied van het hart', zal zowel in het privéleven als op het werk een meer gesettelde levensweg worden nagestreefd en aan de klinische opleiding worden begonnen. Al blijft het bloed kruipen waar het niet gaan kan…

name: Marc A. Brouwer
date of birth: March 24th 1971, Bussum
address: St. Annastraat 37, 6524 EE Nijmegen

Education

1977	Elementary School: Rehobothschool, Naarden-Vesting.
1983	College at A-levels: Willem de Zwijger College, Bussum.
1989	Medicine, Free University, Amsterdam.
1994	University degree, preclinical program medicine, cum laude.
1997	M.D. degree, cum laude.

Research activities

1990-1993	APRICOT long-term follow-up project Department of Cardiology, Free University Hospital Amsterdam Supervision: Dr. A. Meyer en Prof. Dr. F.W.A. Verheugt
1993-1994	Grant awarded by The Netherlands Heart Foundation MITI prehospital thrombolysis project, Seattle, Washington, USA Supervision: Dr. W. Douglas Weaver
1998-2004	Research fellow: the APRICOT trials Department of Cardiology, University Medical Center Nijmegen Realization of an APRICOT database subset for the Antithrombotic Trialists' Collaboration, Oxford, United Kingdom
2000	Hotline Session ESC 2000, Amsterdam: presentation APRICOT-2 trial
2000-2004	Supervision of and participation in PhD projects of several research fellows

2002-2003 Initiation international collaboration: Auckland Hospital New Zealand
Research supervision: Professors Dr. J. K. French, Dr. H. D. White

Reviewer European Heart Journal

2004 Two research grants awarded by the Netherlands Heart Foundation
- Study on Aspirin Resistance in major Antithrombotic Trials: SARA
- The APRICOT-3 trial

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